STUDY PROTOCOL

Therapist Education and Massage for Parent Infant-Outcomes (TEMPO)

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Short Title: TEMPO

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I confirm that I have read this protocol and understand it.

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Date: 10/17/19

Summary of Changes from Previous Version (Version 1.0, 10 May 2019)

Affected Section(s)	Summary of Revisions Made
Protocol Synopsis, 2.1, 6.1	Modified Aim 1, P5 to add “and weekly and bi-weekly reporting of physical therapy interventions (goal ≥ 50%)”.
Protocol Synopsis, 3.1	All IRB-approved study team members can approach potential participants.
1.2, 1.3, 3.1, 4.3, 7	Removed text messaging from study procedures
1.3, 3.1, 4.2, 4.3, 4.4, 5, 6.2	Removed Spielberg State Trait Anxiety Inventory (STAI) from evaluation tools for parent measures
1.3, 3.1, 4.2, 4.3, 4.4, 5, 6.2	Added the Acceptability of Intervention Measure (AIM), Feasibility of Intervention Measure (FIM), and/or Patient-Reported Outcomes Measurement Information System (PROMIS) Adult Profile Short Form – Anxiety to evaluation tools for parent measures.
2.1	Clarified primary objectives
4.2, 4.3, 9	Added methods for parents to record frequency of administered interventions
5	Modified salivary cortisol procedures – only Principal Investigator will collect buccal swab
6.1	Defined acceptability and feasibility for statistical considerations
Entire Document	Corrected formatting and typographical errors

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
TEMPO	Therapist Education and Massage for Parent-Infant Outcomes
PT	Physical Therapist
EP	Extremely Preterm
PTI	Physical Therapy Interventions
NCCC	Neonatal Critical Care Center
CRF	Case Report Form
AE/SAE	Adverse Event/Severe Adverse Event
NCCIH	National Center for Complimentary and Integrative Health

PROTOCOL SYNOPSIS

Study Title	TEMPO: A feasibility study of a physical therapist-led program for parents of extremely preterm infants
Funder	National Center for Complimentary and Integrative Health
Clinical Phase	Feasibility
Study Rationale	The TEMPO program is a structured, therapist-led PT program developed by the applicant based on her clinical experience. TEMPO trains and supports parents to deliver PTIs such as massage and developmental play during hospitalization and in the home setting. The goal of this project is to assess the feasibility and acceptability of TEMPO for parents of EP infants born in the Neonatal Critical Care Center (NCCC) at UNC Children's Hospital.
Study Objective(s)	Aim 1. Evaluate feasibility by using the sample to estimate the following population parameters: P1 In the target population, the % of eligible dyads who would consent to enroll (goal ≥ 55%) P2 In the target population, the % of enrolled dyads who would consent to randomization (goal ≥ 70%) P3 In the target population, the % of enrolled dyads who would complete all protocol components (goal ≥ 70%) P4 In the target population, the % of enrolled dyads who would participate for the full 12 months (goal ≥ _70%) P5 In the target population, the % of enrolled dyads who would provide complete data and interviews (goal ≥ 70%) and weekly and bi-weekly reporting of physical therapy interventions (goal ≥ 50%) P6 In the target population, the % of enrolled dyads who would perform physical therapy interventions at least 2-to-3x/week (goal ≥ 70%) Aim 2. Use results from Aim 1 to refine the TEMPO intervention. Aim 3. Use the sample data to estimate of population parameters needed for planning a future study; specifically, estimates of means, standard deviations, and serial correlations of the distributions of the following variables: infant salivary cortisol, parent salivary cortisol, the parent questionnaire scores, and infant CTS and BSID scores.
Study Design	Prospective single group, non-randomized study
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria: Infants with gestational age <28 weeks gestation, within the first 3 weeks of life, and their biologic mother or father. Parent must be able to speak and understand English. Exclusion Criteria: Infants who do not have a biological parent available to consent within the first 3 weeks of life. Infants with genetic/chromosomal abnormality, congenital neurological or musculoskeletal disorder, or abnormal bone density that would affect the ability to do massage and/or exercise and the safety of the infant. Parents who are unwilling to engage in all components of TEMPO.

Number Of Subjects	30 infant-parent dyads
Study Duration	Each parent-infant dyad's participation will last approximately 15 months. The entire study is expected to last approximately 27-28 months.
Study Phases Screening Study Treatment Follow-Up	• Screening: Once a PT referral is received for an infant born at <28 weeks gestation, the PI will be notified by the receiving therapist and an IRB-approved study team member will approach the biologic mother and/or father of the infant to discuss the study. • Intervention: The components of TEMPO are evidence-based and include infant massage, PTIs including developmental support and play activities to promote infant behavioral-motor development, principles of family-centered care, and multiple modes of educational delivery to enhance parent retention of knowledge and confidence in continuing PTIs after discharge. • Follow-Up: Follow-Up after hospital discharge will include clinic visits at 2 and 12 months corrected age.
Safety Evaluations	The physical therapist, with the assistance of the bedside nurse, will monitor vital signs continuously (heart rate, oxygen saturation, and respiratory rate) during all massage and physical therapy interventions. If the infant demonstrates any of negative responses during massage or PTIs, then the PT will adjust the treatment session accordingly to focus on developmental support that the infant can tolerate, while continuing to educate the parent about their infant's cues and behavior.
Statistical And Analytic Plan	Because the goal of this study is to assess feasibility and acceptability of the TEMPO program, we are not collecting the validated outcome measures (eg. Surveys, interview data, and infant motor assessment scores) to estimate the effectiveness of TEMPO; rather our goals are to: (1) assess the feasibility of completing each measure and (2) estimate the means and standard deviations as the basis for sample size calculations for future clinical trials.
DATA AND SAFETY MONITORING PLAN	• Independent monitor will review progress reports (patient recruitment, retention/attrition, and AEs) quarterly • Annual Report sent to Independent Monitor • Copy of Annual Report and Independent Monitor's recommendations sent to NCCIH annually • The PI will carefully review study documentation on a weekly basis to ensure data collection from study subjects is complete. • Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents.

1 BACKGROUND AND RATIONALE

1.1 Introduction

The Therapist Education and Massage for Parent-Infant Outcomes program (TEMPO) is a structured, therapist-led PT program developed by the applicant based on her clinical experience. TEMPO trains and supports parents to deliver PTIs such as massage and developmental play during hospitalization and in the home setting. The goal of this project is to assess the feasibility and acceptability of TEMPO for parents of EP infants born in the Neonatal Critical Care Center (NCCC) at UNC Children's Hospital.

There are several innovative aspects to this research. First, the TEMPO program enhances standard care by structuring the nature and frequency of therapist-parent interactions to increase the parent's comfort level with administering massage and developmental activities with their EP infant. In standard care, parent education during hospitalization is provided spontaneously if the parent is available, does not include infant massage, does not use supplementary written materials or resources, and does not include check-ins with a therapist post-discharge. Second, this project will recruit parents of infants <28 weeks gestation, a population that has not been studied in previous research on massage. Third, the TEMPO program emphasizes the critical role therapists can have not only in educating and supporting parents of EP infants, but in developing and rigorously testing complementary/integrative health approaches in unique patient populations. Finally, once TEMPO is further developed it can be adapted to evaluate other complementary/integrative health approaches for the EP population and other high-risk infant populations (e.g., neonatal drug withdrawal, infants with hypoxic ischemic encephalopathy).

1.2 Name and Description of Investigational Product or Intervention

The Therapist Education and Massage for Parent-Infant Outcomes program is evidence-based and includes infant massage,[1,8,9] PTIs including developmental support and play activities to promote infant behavioral-motor development,[5,6] principles of family-centered care,[5] and multiple modes of educational delivery[6] to enhance parent retention of knowledge, parent-infant bonding, and confidence in continuing PTIs after discharge. TEMPO includes these components:

- Early Parent Education Session
- Weekly Parent Education Sessions
- Infant Massage Parent Education Sessions
- Discharge Parent Education Session
- Parent Education Post-Discharge
- Bi-weekly emails
- 2 Month Follow-up Massage Review Session

1.3 Non-Clinical and Clinical Study Findings

<u>Potential Benefits related to TEMPO intervention:</u>

- Parent becoming more comfortable touching, holding, and playing with your infant from a very young age during hospitalization
- Parent feeling confident in your ability to read your infant's body language and needs as they change during hospitalization
- Increased opportunities for infant-parent bonding

- Learning how to perform infant massage with your infant which has many benefits for parent (eg. reducing stress and depression) and for infant (eg. gaining weight and staying calm)
- Parent may develop a strong relationship with the therapy team in the NCCC and will receive weekly updates about your infant's motor progress
- Parent will continue to receive therapist tips about infant development after discharge home
- Parent will receive a one-on-one infant massage review session after discharge home
- Parent will have the opportunity to reflect on sense of parent competence during the first year of infant's life

Risks related to TEMPO intervention:

- Infant autonomic instability/stress, discomfort, or skin reaction as a result of Vaseline or Aquaphor during the massage session
- Inconvenience or stress to parents from weekly meetings with therapist and/or completion of questionnaires
- Psychological distress of parents when learning about preterm development or if the infant does not have a positive response to massage
- Breach of confidentiality if emails are seen by other persons than the parent, or if data from the medical record is breached

1.4 Relevant Literature and Data

Physical therapists (PTs) play a major, but often unrecognized role, in supporting extremely preterm (EP) infants and their parents through non-pharmacologic and developmentally-supportive care during and after long-term hospital stays. While there is strong evidence to support that physical therapy interventions (PTIs) improve, or even cure, a number of pediatric conditions (e.g. torticollis), there is little data demonstrating how PTIs done in the NICU setting influence outcomes in EP infants or whether there is benefit to parents continuing PTIs after hospital discharge. In addition, the clinical experience of the applicant suggests that parents can be taught how to do PTIs with their infant and doing so may be an important contributor to increasing parent confidence in taking care of their infant. This is especially important because parents of EP infants experience a challenging transition to parenthood and often experience increased levels of stress, depression, and fear of incompetence in caring for their child compared to parents of non-EP infants.[1] Over the long-term, these issues can negatively impact parent-infant bonding[2] and parent quality of life.[3] In addition, decreased parental bonding and attention can effect motor outcomes of the infant.[4]

The extra-uterine environment presents significant challenges for infants born extremely preterm (EP). In the NCCU, physical therapists provide ongoing assessment of infant development and deliver interventions designed to mitigate the behavioral-motor effects of preterm birth.[5] This presents a unique opportunity for PTs to foster parental involvement in their infant's care by teaching parents how to respond to their infant's behavioral cues and to facilitate their infant's motor development through techniques such as massage.[6] Massage has been shown to be safe,[1] is associated with many benefits for EP infants,[7] and has been shown to be beneficial in decreasing parent depression[1] and anxiety.[8,9] However, the applicant's clinical experience is that despite being taught how to administer massage by the PT during admission, parents do not regularly continue this practice. Because of the potential benefits to parents in terms of decreased stress, anxiety and an increased sense of parent-infant bonding, there is a critical need to find more feasible ways to teach and support parents to deliver massage and other PTIs throughout the infant's hospitalization and post-discharge. TEMPO has been developed to address this need.

Established Validity for Scales and Evaluation Tools

Parent Measures

- Acceptability of Intervention Measure (AIM): A 12 item implementation outcome assessment designed to measure if the intervention is perceived as agreeable, palatable, or satisfactory.[11]
- Feasibility of Intervention Measure (FIM): A 9 item implementation outcome assessment designed ot measure the extent to which a new treatment can be successfully used or carried out.[11]
- Patient-Reported Outcomes Measurement Information System (PROMIS) Adult Profile Short Form - Anxiety: The PROMIS Anxiety short form is a valid and reliable measurement tool used to assess self-reported fear, anxious misery, hyperarousal, and somatic symptoms related to arousal.[12]
- Centers for Epidemiologic Studies Depression Scale (CESD): A valid, reliable self-assessment tool for evaluating depressive symptoms in adult populations, including among mothers during and after parturition.[13] The CESD 20-item scale will be used.
- Edinburgh Postnatal Depression Scale (EPDS): A 10-item self-report questionnaire validated to detect change in depressive symptoms in mothers both during and after the postnatal period.[14] EPDS ratings in parents have been correlated with scores of infant temperament as measured by the Carey Temperament Scale, and shown to improve with massage.[13]
- Parenting Sense of Competence Scale (PSOC): A 17-item scale to assess satisfaction of parenting and parental self-efficacy in a variety of populations,[15] with higher scores indicating a greater sense of parental self-efficacy.
- Postnatal Attachment Questionnaire (PAQ): A postnatal questionnaire with 4 components: pleasure in proximity, tolerance, need-gratification and protection, and knowledge acquisition designed to query the parents' feelings about their infants under 1 year of age.[16] This questionnaire is associated with the Attachment Q-set (ASQ), an observational assessment of infant-parent bonding.[16]
- Salivary Cortisol: Salivary cortisol is a biomarker for stress.[17] Salivary cortisol concentrations (ng/dl) may be used to understand the mechanism by which TEMPO impacts physiological stress states.

Infant Measures

- Salivary Cortisol: Salivary cortisol is a biomarker for stress.[17] Salivary cortisol concentrations (ng/dl) may be used to understand the mechanism by which TEMPO impacts physiological stress states.
- Carey Temperament Scales (CTS): This questionnaire assesses nine temperamental characteristics of infants. Caregivers are presented with a statement describing a certain behavior and asked to rate how often their child behaves in that way on a scale from 1 (almost never) to 6 (almost always), with higher scores indicating more difficult temperament.[13]
- Bayley Scales of Infant Motor Development-III (BSID-III): A standardized assessment to evaluate cognitive development, expressive and receptive language, and fine and gross motor development in children between the ages of 1 month and 42 months.[18] This assessment will be completed at the 12 month corrected at follow-up visit.

2 STUDY OBJECTIVES

The goals of this project are to test feasibility and acceptability of the TEMPO program and study protocol.

2.1 Primary Objective

To conduct a pilot study to demonstrate TEMPO's feasibility as assessed by:
P1 In the target population, the % of eligible dyads who would consent to enroll (goal ≥ 55%)
P2 In the target population, the % of enrolled dyads who would consent to randomization (goal ≥ 70%)
P3 In the target population, the % of enrolled dyads who would complete all protocol components (goal ≥ 70%)
P4 In the target population, the % of enrolled dyads who would participate for the full 12 months (goal ≥ _70%)
P5 In the target population, the % of enrolled dyads who would provide complete data collection and interviews (goal ≥

70%) and weekly and bi-weekly reporting of physical therapy interventions (goal ≥ 50%)
P6 In the target population, the % of enrolled dyads who would perform physical therapy interventions at least 2-3x/week (goal ≥ 70%)

Secondary Objectives

Based on the quantitative and qualitative data from Aim 1, refine TEMPO to facilitate parent-administered physical therapy and massage during neonatal intensive care hospitalization and after discharge.

Additionally, we will use the sample data to estimate of population parameters needed for planning a future study; specifically, estimates of means, standard deviations, and serial correlations of the distributions of the following variables: infant salivary cortisol, parent salivary cortisol, the parent questionnaire scores, and infant CTS and BSID scores.

3 INVESTIGATIONAL PLAN

3.1 Study Design

Type of design: This is a prospective single group, non-randomized study designed to determine the feasibility and acceptability of TEMPO. The TEMPO program as part of this study would be offered in addition to standard of care physical therapy intervention in the NCCC. Standard of care physical therapy in the NCCC involves 1-2 PT sessions weekly, spontaneous (unplanned) parent education as the parent is available in the hospital, and follow up outpatient clinic visits with a PT.

Screening/Baseline:

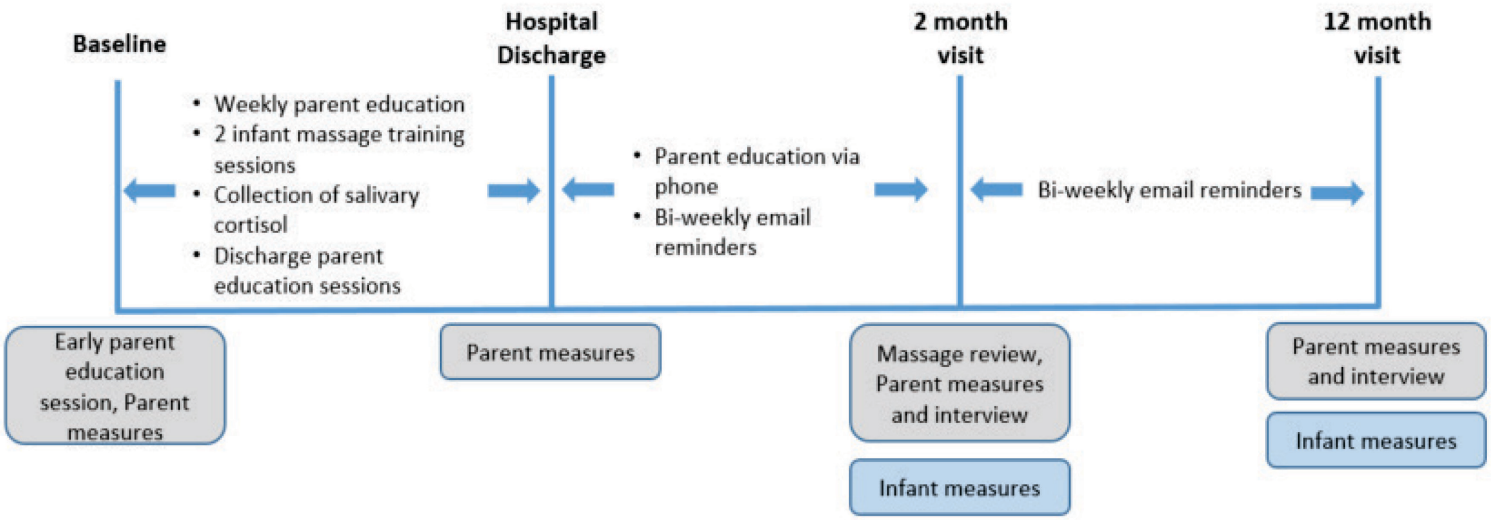
The recruitment process with the parents will be initiated once the physical therapy referral has been made by the treating physician. The neonatology provider team will receive an introduction to the study from the PI (McCarty) and chief neonatologist/grant mentor (O'Shea) prior to study initiation. All infants who meet eligibility criteria for the study also receive standard physical therapy orders in the Newborn Critical Care Center (NCCC). A physical therapist attends weekly developmental rounds in the NCCC and participates in the physical therapy referral process by screening patients who are under a certain age and weight. The physical therapy referral is received when the infant is clinically stable and thus should avoid the initial parent distress and need for orientation after the birth and admission to the NCCC. Once a PT referral is received for an infant born at <28 weeks gestation, the PI will be notified by the receiving therapist and an IRB-approved member of the study team will approach the biologic mother and/or father of the infant to discuss the study. In order to ensure that parents have sufficient time to consider participation, the study team member will contact the family at the bedside or by phone call once the physical therapy referral has been initiated to introduce the TEMPO study. The study team member will offer to leave the consent document with the parent(s). An IRB-approved member of the study team will always be available to answer any questions related to the informed consent, and if they express interested in participating, then informed consent will be obtained.

Intervention/Treatment and Follow up: Please see Table 1 and Figure 1 below for information regarding the timing and sequence of intervention and follow up. Additional detail regarding the study intervention can be found in sections 4 and 7.

Table 1: Study Events

Event	Baseline	During Hospital Admission	Hospital Discharge	Post discharge	First F/U visit	F/U at 12 mos visit
Parent measures: (AIM, FIM, PROMIS, CESD, EPDS, PSOC)	x		x		x	x
PAQ						x
Parent Interview					x	x
Parent Education Sessions	x	x	x			
Salivary cortisol pre and post massage		x				
Weekly Parent Education including massage		x				
Email				bi-weekly		
Massage Review					x	
Infant measures					x	x

Figure 1: Study Scheme



3.2 Study Duration, Enrollment and Number of Subjects

Study Duration:

Enrollment and Number of Subjects: The study will be conducted in the Neonatal Critical Care Center at UNC Children's Hospital where approximately 100 EP infants (<28 weeks gestation) are born each year. Of these infants, approximately 75% will survive, and approximately 57 of these infants will meet eligibility criteria. Our goal is to enroll 55% of eligible infants-parent dyads, and therefore our proposed sample size is 30 dyads, but will enroll up to 40 dyads over the period of 12 months.

3.3 Study Population

Inclusion Criteria: Infants with gestational age <28 weeks gestation, within the first 3 weeks of life, and their biologic mother or father. Must be able to speak and understand English.

Exclusion Criteria: Infants who do not have a biological parent available to consent within the first 3 weeks of life. Infants with genetic/chromosomal abnormality, congenital neurological or musculoskeletal disorder, or abnormal bone density related to a congenital condition that would affect the ability to do massage and/or exercise and the safety of the infant. Parents who are unwilling to engage in all components of TEMPO.

4 STUDY PROCEDURES

4.1 Screening/Baseline Visit procedures

At the baseline visit, the therapist will provide parent education (as described in section 7, *Early Parent Education*), and the parent will complete baseline surveys (as described in section 1.4) on the study iPad. While both parents may elect to receive training in the intervention, they will be asked to designate one parent who is the most likely to perform the intervention after discharge and this same parent should complete all the parent interviews and questionnaires. Please see Table 1: Study Events and Figure 1: Study Scheme in the Appendix for a complete timeline.

4.2 Intervention/Treatment procedures (by visits)

The TEMPO program involves components during and after hospitalization.

During infant hospitalization

- ***Visit 1: Early Parent Education Session:*** Initiated within 3 weeks of infant birth. The PT will educate the parent about the importance of infant positioning, the impact of prematurity on the motor and sensory systems, and how to read and respond to infant behavioral-motor cues[5] using a written pamphlet with pictures to supplement the verbal education lasting about 30 minutes.
    - At this visit, the therapist will have the parent fill out the following questionnaires for baseline measurement: AIM, FIM, PROMIS, CESD, EPDS, PSOC
    - The therapist will also ask the parent to complete a contact information form and a demographic form.
- ***Visits 2-8: Weekly Parent Education Sessions <34 weeks:*** Following the initial parent education session, the PT will hold weekly parent education sessions, ideally at the time of therapy. When the infant is this young (<34 weeks gestation), PT intervention and education will focus on infant behavioral-motor cues, reading/response to infant cues, positioning strategies/concerns, and developmentally appropriate stimulation of the infant. If the parent is not available for all therapy sessions, then the parent will receive a weekly update about their infant's progress face-to-face and/or via video chat.
    - Parents will be asked to record the frequency of physical therapy interventions on a bedside card.
- ***Visits 9-10: Infant Massage Parent Education Sessions:*** Parent-administered infant massage will be incorporated into the therapy plan of care as soon as the infant's medical provider determines that the infant is physiologically stable and can tolerate massage. This time is generally once the infant is approximately 34 weeks gestational age, approximately 1500 grams, and is demonstrating temperature stability out of the isolette for short periods. At a minimum, the therapist will teach massage for the back or lower extremities over 2 parent education sessions. The therapist will demonstrate massage strokes on a doll using verbal cues to guide the parent while the parent administers massage on the infant. An instructional massage pamphlet will be provided. Once the therapist has determined parent safety with massage administration, parents will be encouraged to practice infant massage when they visit the baby and to note when they do this by marking a card at the bedside.

    - Pre and Post both massage sessions, the PI or study coordinator will collect salivary cortisol via buccal swab as a measure of physiologic stress.
- ***Visits 11+: Weekly Parent Education Sessions >34 weeks:*** Weekly parent education once the infant is >34 weeks will begin to incorporate hands-on developmental play activities, introduction to visual engagement, and postural control practice in variety of positions that the infant tolerates. Additionally, the PT and parent may choose to review massage at these visits. If the parent is not available for all therapy sessions, then the parent will receive a weekly update about their infant's progress face-to-face and/or via video chat.
    - Parents will be asked to record the frequency of physical therapy interventions on a bedside card.
- ***Final Visit during hospitalization:*** Within the week of hospital discharge, the PT will schedule a face-to-face parent education session lasting about 30 minutes to review age-appropriate developmental play activities for home and review infant massage. A supplemental handout and therapist email and pager information will be provided.
    - At this visit, the therapist will have the parent fill out the following questionnaires for ongoing measurement: AIM, FIM, PROMIS, CESD, EPDS, PSOC (Aim 1).

4.3 Follow- up procedures (by visits)

The TEMPO program has additional components that extend beyond the hospital period. Parent and infant outcome measures will be collected at the first follow-up and 12 month corrected age follow-up clinic visits. Please see Table 1: Study Events and Figure 1: Study Scheme in the Appendix for a complete timeline.

After hospitalization:

- ***Visit 1: Parent Education Post-Discharge:*** The PT will call the parent within 2 weeks of discharge to follow up about discharge education and massage. During this phone call, the PT will review the home program and massage techniques. The PT will also answer any parent questions. Therapist email and pager information will be provided.
- ***Visits 2-12 (approximate): Bi-weekly emails:*** The PT will send bi-weekly emails with developmental play activity and massage reminders and tips from hospital discharge through the first follow up appointment.
    - These emails will include a link for parents to report frequency of PT intervention and massage at home.
- ***Visit 13 (approximate): First Visit Follow-up Massage Review Session:*** At the infant's first follow-up appointment with the multidisciplinary neonatology team, the PT will provide a gross motor screening assessment and education. In addition, as part of the TEMPO program, a PT will facilitate a parent-administered infant massage session to provide an opportunity for parent to receive feedback on technique from the PT. This session will address any safety concerns, infant changes, and parent questions.
    - At this visit, the therapist will have the parent fill out the following questionnaires for ongoing measurement: AIM, FIM, PROMIS, CESD, EPDS, PSOC
    - At this visit, the PI or study coordinator will interview the parent about acceptability of the TEMPO program.
- ***Visits 14+ (approximate): Bi-weekly emails:*** The PT will continue to send bi-weekly emails with developmental play activity and massage reminders until the 12 month follow up appointment.
    - These emails will include a link for parents to report frequency of PT intervention and massage at home.
- ***12 Month Follow-up Appointment:*** At the standard of care 12 month corrected age follow-up appointment with the multidisciplinary neonatology team, the PT will administer a standardized assessment of gross and fine motor skills (Bayley Scales of Infant Development-III).
    - At this visit, the therapist will have the parent fill out the following questionnaires for ongoing measurement: AIM, FIM, PROMIS, CESD, EPDS, PSOC (Aim 1)

- Additionally, the parent will complete the PAQ questionnaire. (Aim 1)
- At this visit, the PI or study coordinator will interview the parent about acceptability of the TEMPO program. (Aim 1, Aim 2)

4.4 Subject Completion/ Withdrawal procedures

The study staff will inform the subject when his/her participation has come to an end and will document the discussion in the study record. If the infant is transferred to an outside hospital prior to discharge home, then the parents will be asked to complete the parent measures (PROMIS, CESD, EPDS, PSOC) at that time instead of hospital discharge. If the parent chooses to withdraw their infant for any reason, the parent does not have to complete the above measures.

An infant may no longer participate in the study under any of the following circumstances:

- The medical condition of the infant deteriorates and the medical team no longer recommends PT or massage
- The infant experiences a severe AE or SAE related to the intervention
- The Parent is no longer interested in participating

In the event that an infant has an AE related to massage medium (Aquaphor), then massage will be performed without the medium once the skin has healed.

5 STUDY EVALUATIONS AND MEASUREMENTS

Variables that will be abstracted from medical charts:

- **Infant:**
- Name
- Date of birth
- Gestational age at birth
- Birth weight
- Race/ethnicity
- Salivary Cortisol (post-salivary swab test)

- **Parent:**
- Name
- Age
- Race/ethnicity
- Highest education completed (if available)
- Salivary Cortisol (post salivary swab test)

Parent Measures

- Acceptability of Intervention Measure (AIM): A 12 item implementation outcome assessment designed to measure if the intervention is perceived as agreeable, palatable, or satisfactory.
- Feasibility of Intervention Measure (FIM): A 9 item implementation outcome assessment designed ot measure the extent to which a new treatment can be successfully used or carried out.
- Patient-Reported Outcomes Measurement Information System (PROMIS) Adult Profile Short Form - Anxiety: The PROMIS Anxiety short form is a valid and reliable measurement tool used to assess self-reported fear, anxious misery, hyperarousal, and somatic symptoms related to arousal.
- Centers for Epidemiologic Studies Depression Scale (CESD): The CESD 20-item scale will be used.
- Edinburgh Postnatal Depression Scale (EPDS): A 10-item self-report questionnaire validated to detect change in depressive symptoms in mothers both during and after the postnatal period.
- Parenting Sense of Competence Scale (PSOC): This measure will be used to assess change in the parent's sense of competence in caring for their infant throughout the study period.

- Postnatal Attachment Questionnaire (PAQ): This questionnaire is associated with the Attachment Q-set (ASQ), an observational assessment of infant-parent bonding, and will serve as a measure of the parent emotional component of infant-parent bonding in the follow-up stage of the study period.
- Salivary Cortisol: Salivary cortisol is a biomarker for stress. Salivary cortisol concentrations (ng/dl) may be used to understand the mechanism by which TEMPO impacts physiological stress states. The PI or research coordinator will swab the parent's buccal mucosa immediately pre- and post-massage at the first massage education session.
- Parent Interview: The parent who performed the study intervention will be interviewed at the first follow-up visit and the 12-month follow-up visit to obtain their insights on the feasibility, acceptability and perceived benefit of TEMPO. The PI or study coordinator elicit their feedback on program materials, intervention components, and factors that influenced whether they were able to continue the protocol at various time points post-discharge. For example: what they liked or disliked about the program, how often they did massage and for how long, did they find the massage easy to do on an ongoing basis, do they have suggestions to improve feasibility? We will also ask about willingness to have participated in this study if it were a randomized trial. This information will be critical to develop the planned trial (Aim 1 and 2). For example, should a parent not be willing to be randomized, the trial may need to randomize at some level other than individual infants/parents (e.g., hospital or a waitlist control condition).

Infant Measures

- Salivary Cortisol: Salivary cortisol will be collected by PI via buccal swab immediately pre- and post-massage at the first massage education session.
- Carey Temperament Scales (CTS): This questionnaire assesses Infant temperament to better understand if infant temperament may be influenced by massage and is associated with parent-infant bonding.
- Bayley Scales of Infant Motor Development-III (BSID-III): A standardized assessment provided by a developmental specialist (physical or occupational therapist in our study) to evaluate cognitive development, expressive and receptive language, and fine and gross motor development in children between the ages of 1 month and 42 months.

5.1 Safety Evaluations

The infant will be monitored for safety throughout all PT sessions. With the assistance of the bedside nurse, vital signs will be monitored continuously (heart rate, oxygen saturation, and respiratory rate) during all massage and physical therapy interventions. The massage or PTIs will be stopped if the infant's heart rate exceeds 200 beats per minute, if the infant's oxygen saturation drops <90%, or respiratory rate exceeds 90 breaths per minute without spontaneous recovery or response to strategies employed by the PT or nurse to resolve. Additionally, the PT will monitor infant behavioral-motor cues for signs of overstimulation or stress during massage and PTIs in order to promote a positive experience for the infant and parent. If the infant demonstrates any of these negative responses during massage or PTIs, then the PT will adjust the treatment session accordingly to focus on developmental support that the infant can tolerate, while continuing to educate the parent about their infant's cues and behavior.

Prior to the parent education for massage session, the PT will test a small area of the infant's skin (likely on the lower leg or back) to assess any negative skin reaction to Aquaphor, the medium used for massage. If after 24 hours of monitoring, the infant does not develop skin irritation, then the PT will proceed with an introductory massage session. If the infant has a skin reaction to Aquaphor, then the PT will determine an alternative medium for massage in consultation with the medical team and the skin care nurse. Infant massage will first be administered by the PT to determine the infant's tolerance prior to the parent education for massage session.

The study team will generate Study Reports for the Independent Monitor and will provide information on the following study parameters: screened and enrolled parent-infant dyads, unanticipated, serious adverse events, missed study visits and dyads that are lost to follow-up.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Objectives

No hypothesis tests will be performed in this study. The primary goal of this project is to test feasibility and acceptability of the TEMPO program and study protocol (Aim 1). As such, the analysis plan will not focus on inferential statistics but on measures of feasibility identified in the NCCIH's *Framework for Developing and Testing Mind and Body Interventions*[10] (https://nccih.nih.gov/grants/mindbody/framework):

- Recruitment: Percentage of eligible infant-parent dyads who enroll in the study (Goal ≥55%)
- Willingness to be randomized: Percentage of enrolled parents who, in interviews, report they would agree to be randomized (Goal ≥70%)
- TEMPO delivered per protocol: Percentage of enrolled parents who complete all TEMPO components per protocol (Goal ≥70%) and weekly and bi-weekly reporting of physical therapy interventions (goal ≥ 50%).
- Retention: Percentage of enrolled parents who are retained in the study at 12 months (Goal ≥70%), reasons for attrition for those who do not complete the protocol
- Complete data collection: Percentage of enrolled parents who complete data collection, including interviews (Goal ≥70%)
- Adherence: Percentage of enrolled parents who complete at least 2-3x/week during hospitalization and 2-3x/week in-home PTIs as noted on the parent log or survey (Goal ≥70%)
- Acceptability and Feasibility of TEMPO: Percentage of parents who rate acceptability and feasibility as 4/5 or 5/5 using the Acceptability of Intervention Measure and the Feasibility of Intervention Measure (Goal ≥70%)
- Acceptability of the Protocol: A structured interview guide will be followed by the PI or research coordinator. Interviews will be audio recorded and transcribed by a confidential online service. All audio files will be stored and transmitted using TLS 1.2 encryption for a high level of security. Interviews will be coded by the PI for content and qualitative analysis to derive themes. (Aim 1 and 2)

6.2 Secondary Objectives

Additionally, we plan to estimate the means and standard deviations as the basis for sample size calculations using the following measures for future clinical trials.

Parent Measures

- PROMIS Adult Short Form - Anxiety
- Centers for Epidemiologic Studies Depression Scale (CESD)
- Edinburgh Postnatal Depression Scale (EPDS)
- Parenting Sense of Competence Scale (PSOC)
- Postnatal Attachment Questionnaire (PAQ)
- Salivary Cortisol
- Parent Interview

Infant Measures

- Salivary Cortisol

- Carey Temperament Scales (CTS)
- Bayley Scales of Infant Motor Development-III (BSID-III)

6.3 Statistical Methods

In addition to the analysis plan above, we will calculate the mean and standard deviation of each potential outcome measure to estimate the sample size required for a randomized trial. All statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CIs) (Aim 1). We will combine that information with what we learn from parent interviews as the basis for selecting primary and secondary outcomes for future randomized trials to evaluate TEMPO (Aim 2).

Although validated outcome measures will be collected in this pilot study in order to refine the TEMPO protocol for future study, these variables will not be incorporated in the statistical analyses of outcomes. Collection of the validated measures will also be used to select a sample size for a full study (Aim 3). We anticipate this data will be used to develop estimates of correlations among repeated measures, means and standard deviations. Point-estimates of the means, standard deviations, and correlations will be tabulated along with corresponding confidence intervals (Aim 3).

6.4 Interim Analysis

Apart from safety monitoring, no interim analyses will be performed.

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Every 2 weeks	PI
	Quarterly	Independent Monitor
Status of all enrolled subjects, as of date of reporting	Monthly	PI
	Quarterly	Independent Monitor
Data entry quality control checks on 20% of charts	Quarterly	PI
Adherence data regarding study visits and intervention	Monthly	PI
	Quarterly	Independent Monitor
AEs	Monthly, within 24 hours	PI
	Quarterly, within 24 hours	Independent Monitor
	Annually	NCCIH
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitor NIH/NCCIH

Unanticipated Problems	Monthly	PI
	Per Policy	IRB, NCCIH

7 STUDY INTERVENTION

- ***Early Parent Education Session:*** Initiated within 3 weeks of infant birth. The PT will educate the parent about the importance of infant positioning, the impact of prematurity on the motor and sensory systems, and how to read and respond to infant behavioral-motor cues[5] using a written pamphlet with pictures to supplement the verbal education lasting about 30 minutes.
- ***Weekly Parent Education Sessions <34 weeks:*** Following the initial parent education session, the PT will hold weekly parent education sessions, ideally at the time of therapy. When the infant is this young (<34 weeks gestation), PT intervention and education will focus on infant behavioral-motor cues, reading/response to infant cues, positioning strategies/concerns, and developmentally appropriate stimulation of the infant. If the parent is not available for all therapy sessions, then the parent will receive a weekly update about their infant's progress face-to-face and/or via video chat.
- ***Infant Massage Parent Education Sessions:*** Parent-administered infant massage will be incorporated into the therapy plan of care as soon as the infant's medical provider determines that the infant is physiologically stable and can tolerate massage. At a minimum, the therapist will teach massage for the back or lower extremities over 2 parent education sessions – one early session in the isolette (if necessary) and one later session out of the isolette. The therapist will demonstrate massage strokes on a doll using verbal cues to guide the parent while the parent administers massage on the infant. An instructional massage pamphlet will be provided. The massage intervention is comprised of moderately firm effleurage strokes on the extremities for periods of 10-20 minutes followed by gentle passive muscle elongation. Use of upper or lower body swaddle, pacifier, and room darkening may be necessary to achieve positive infant responses during massage.
- ***Visits 11+: Weekly Parent Education Sessions >34 weeks:*** Weekly parent education once the infant is >34 weeks will begin to incorporate hands-on developmental play activities, introduction to visual engagement, and postural control practice in variety of positions that the infant tolerates. Additionally, the PT and parent may choose to review massage at these visits. If the parent is not available for all therapy sessions, then the parent will receive a weekly update about their infant's progress face-to-face and/or via video chat.
- ***Discharge Parent Education Session:*** Within the week of hospital discharge, the PT will schedule a face-to-face parent education session lasting about 30 minutes to review age-appropriate developmental play activities for home and review infant massage. A supplemental handout and therapist email and pager information will be provided.
    - ***Additional Physical Therapy Intervention Description:*** Age appropriate physical therapy interventions and developmental play activities will be taught to parents during the hospital stay at weekly visits and at the discharge parent education session. These activities may include but are not limited to: Prone positioning to develop head, neck, and shoulder strength, supine play activities like patty-cake and leg bicycles to promote flexion of the trunk and extremities against gravity, visual tracking activities to promote symmetrical movement of the neck/head, and supported sitting activities in the parent's lap to promote postural control.
- ***Parent Education Post-Discharge:*** The PT will call the parent within 2 weeks of discharge to follow up about discharge education and massage. During this phone call, the PT will review the home program and massage

techniques. The PT will also answer any parent questions. Therapist email and pager information will be provided.

- ***2 Month Follow-up Massage Review Session:*** At the standard of care 2-month follow-up appointment with the multidisciplinary neonatology team, the PT will provide a gross motor screening assessment and education. In addition, as part of the TEMPO program, a PT will facilitate a parent-administered infant massage session to provide an opportunity for parent to receive feedback on technique from the PT. This session will address any safety concerns, infant changes, and parent questions.
- ***Bi-weekly emails:*** The PT will continue to send bi-weekly emails with developmental play activity and massage reminders until the 12 month follow-up appointment.
- ***12 Month Follow-up Appointment:*** At the standard of care 12 month follow-up appointment with the multidisciplinary neonatology team, the PT will administer a standardized assessment of gross and fine motor skills (Bayley Scales of Infant Development 3).

8 SAFETY MANAGEMENT

This study will be stopped prior to its completion if: (1) the intervention is associated with AEs that call into question the safety of the intervention in infants <28 weeks gestational age; (2) significantly lower study recruitment or retention than expected that will impact the ability to evaluate feasibility of TEMPO.

Definitions

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.

Unanticipated Problems (UP)

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

- Unexpected in terms of nature, severity, or frequency given (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 subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Adverse Event (SAE)

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Time Period and Frequency for Event Assessment and Follow-Up

An independent monitor has been identified to review enrollment, UPs, and AEs. The study team will send the independent monitor a report on enrollment every 4 months, with the expectation that the independent monitor will provide input on enrollment within 30 days. UPs and AEs will be reported to the independent monitor within 24 hours with the expectation that the independent monitor will provide input on UPs and/or AEs within 5 days.

Characteristics of an Adverse Event

Relationship to Study Intervention

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

- *Definitely Related*: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- *Possibly Related:* An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- *Not Related:* The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Expectedness of SAEs

Massage has been studied extensively in infant born at less than 32 weeks gestation, and reported AEs in the literature are rare. Massage has not been studied as extensively in the extremely preterm infant population (<28 weeks gestation), so we will monitor infant heart rate and respiratory rate continuously during massage intervention, and temperature before and after intervention, as outlined in section 5.1 "Safety Evaluations" section. These risks are addressed in the informed consent document. The study PI, infant's medical team, and the independent monitor will review any AE to

determine if it is expected or unexpected based on characteristics of the event and risk information previously described in the literature.

Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on infant's routine care
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on infant's routine care
3. Severe: significant symptoms requiring invasive intervention; infant requires additional medical attention, significant impact on infant's routine care

Reporting Procedures

Information previously unknown to the UNC IRB that suggests new or increased risk to subjects or others is promptly reportable to OHRE within 7 calendar days of the investigator becoming aware of the information.

Reporting for Multi-Center Trials

This is a single site study.

Unanticipated Problem Reporting

All UPs will be recorded using an "unanticipated problem report form" which will include the following information:

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

To satisfy the requirement for prompt reporting, unanticipated problems will be reported as follows:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Monitor, and NCCIH within 24 hours of the PI becoming aware of the event.

Adverse Event Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitor, IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements. and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

Halting Rules

An infant may no longer participate in the study under any of the following circumstances:

- The medical condition of the infant deteriorates and the medical team no longer recommends PT or massage
- The infant experiences a severe AE or SAE related to the intervention
- The Parent is no longer interested in participating

In the event that an infant has an AE related to massage medium (Aquaphor), then massage will be performed without the medium or with a medium approved by the medical team once the skin has healed.

9 DATA COLLECTION AND MANAGEMENT

Data Monitoring

Study progress and safety will be reviewed on a monthly basis or more frequently as needed. Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitor quarterly. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met eligibility criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and a copy of the Annual Report with the independent monitor's recommendations and comments will be forwarded the NCCIH Program Officer within one month following.
The PI will carefully review study documentation on a weekly basis to ensure data collection from study subjects is complete. This includes vitals (heart rate, oxygen saturation, and respiratory rates) during PTIs and salivary cortisol concentrations (ng/dl) documented in the medical chart, weekly parent reports of bedside PTIs, bi-weekly parent reports of home PTIs, and completeness of any questionnaires given to parents at various points in the TEMPO protocol. The PI will review this documentation for completeness.

Data on adherence to the TEMPO protocol will be reported by the parents on a form at the infant's bedside. This data will be collected weekly by research staff and reviewed monthly by the PI. The PI will determine adherence of parents to the TEMPO protocol by reviewing reported TEMPO intervention targets on the form at the infant's bedside. At each weekly parent education session, the therapist will review the TEMPO interventions and recommended frequency. If the parents are unable to meet the frequency, then barriers to this will be recorded by the therapist and shared with the PI.

No data exists on the frequency of the use of massage and physical therapy interventions at the bedside and at home, but we anticipate that 70% of parents will perform massage and/or physical therapy interventions 2-3x/week at the bedside and at home. If adherence falls below the suggested rate, the PI will convene study personnel to discuss methods for improving adherence.

The data will be collected and managed by the PI and the study coordinator. They should ensure that parent surveys are recorded accurately, completely, and in a timely manner. All surveys will be completed digitally on an iPad to ensure accurate interpretation of data.

Data Management and Confidentiality

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the PI. All source documents and laboratory reports must be reviewed by the PI and/or study coordinator, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the PI within 24 hours of being made aware of the event.

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents will be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems must be reviewed by the investigator or designee.

A web-based data management system will be built in REDCap for use in for this study. This data management system provides all of the capabilities required for research data management, including: data transfer, data entry, data validation, database updating, database closure, data retrieval, data inventory, security and confidentiality, and archiving. This database is virtually encrypted. The database will be secured with password protection. Information that is entered into the database will be coded using study identification numbers. Any electronic communication with outside collaborators (e.g. Independent Monitor) will involve only unidentifiable information. The database incorporates an electronic audit trail to show change(s) to data after original entry including the date/time and user making the change.

Direct data entry, where data initially are entered on the screen without having completed a paper form first, will be used when possible; otherwise, paper forms will be utilized and the data will be entered into the REDCap database by a research assistant.

REDCap is housed on a secure, climate-controlled server. UNC has in place an IT Security Plan as required by NIH contracts and grants. As part of the plan, the principle of least access privilege for study files is implemented. Included in the plan are a risk assessment, a system continuity plan, and a disaster recovery plan. Support for REDCap services is provided by the NC TraCS Institute, the Clinical and Translational Science Award center at UNC-CH.

Data confidentiality and security measures will be applied at all levels of TEMPO data acquisition, transfer and storage. REDCap meets exacting data management standards of confidentiality, as well as HIPAA requirements. Beyond the password-controlled access to REDCap, data are encrypted by the system and can only be decrypted for display on-screen by authorized study personnel. Personal identifiers are collected on separate forms as an additional safeguard against linking of identifiers and medical information.

Enrollment and other data management reports will be available from the REDCap database. Monthly reports on study enrollment, intervention, unexpected events, and adverse events will be provided to the principal investigator and

quarterly reports will be provided to the independent monitor. Annual progress reports will be submitted to NIH and to the University of North Carolina IRB.

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

10 RECRUITMENT STRATEGY

The recruitment process with the parents will be initiated once the physical therapy referral has been made by the treating physician. The neonatology provider team will receive an introduction to the study from the PI (McCarty) and chief neonatologist/grant mentor (O'Shea) prior to study initiation. All infants who meet eligibility criteria for the study also receive standard physical therapy orders in the Newborn Critical Care Center (NCCC). A physical therapist attends weekly developmental rounds in the NCCC and participates in the physical therapy referral process by screening patients who are under a certain age and weight. The physical therapy referral is received when the infant is clinically stable and thus should avoid the initial parent distress and need for orientation after the birth and admission to the NCCC. In order to ensure that parents have sufficient time to consider participation, the study coordinator will contact the family at the bedside or by phone call once the physical therapy referral has been initiated to introduce the TEMPO study. The study coordinator will offer to leave the consent document with the parent(s). Once parents feel they have had adequate time to review the informed consent, the informed consent process will proceed.

11 CONSENT PROCESS

The informed consent process is initiated prior to the parent agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to parents. A consent form describing in detail the study procedures and risks will be given to the parent. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or study coordinator will explain the research study to the subject and answer any questions that may arise. The parent will sign the informed consent document prior to any study-related assessments or procedures. Parents will have the opportunity to discuss the study with others or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the parents for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical and research record.

12 PLANS FOR PUBLICATION

At the conclusion of the study period, the data will be analyzed and reviewed by the PI and study team. A manuscript will be drafted and submitted to a multidisciplinary neonatal-perinatal medicine journal in order to reach a variety of audiences.

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