09/10/2024

NEO Rehab Program for Premature Infants at Risk for Cerebral Palsy - NCT04330859

Research protocol: part 1

Project summary

Cerebral Palsy (CP) is the most common motor disability in children born preterm. CP can cause profound disability, lifelong need for extensive care and result in significant economic burden. Ideally interventions should be initiated while at-risk infants are still admitted in the neonatal intensive care unit (NICU), at a stage of rapid brain development where intervention may have an impact on synaptic pruning and brain rewiring. Previous studies indicate that intervention focusing on environmental enrichment and emotional connection between mother and infant can positively impact the neurodevelopmental outcomes of infants born preterm. However, whether this type of interventions can improve the motor outcomes of infants at risk for CP remains unknown. To address this gap in knowledge, we have developed a NICU-based multimodal rehabilitation program (NeoRehab) to support neuromuscular development in preterm infants, This multimodal program, is composed of 6 evidence-based interventions (vocal soothing, scent exchange, comforting touch, kangaroo care, infant massage and physical therapy (PT)) administered in a gestational age (GA) appropriate fashion by a parent. We hypothesize that the NeoRehab program will positively impact short-term motor outcomes in preterm infants at risk for CP. At risk infants (≤32 week's gestation and/or ≤1500 grams birthweight) will be eligible for a pilot randomized controlled trial (RCT) comparing the effects of the NeoRehab program versus usual care on short term motor outcomes (general movements, cranial nerves, posture, movements, tone, and reflexes). **The primary outcome is to determine the acceptability, feasibility and fidelity of the program by performing direct observation, weekly interviews and activity log reviews**. Secondary short-term developmental outcomes will be measured using the Hammersmith Infant Neurological Examination (HINE) instruments, the general movement assessment (GMA), and the Test of Infant Motor Performance (TIMP) at 3 months postmentrual age (PMA). This study addresses one of the priorities of the National Center for Medical Rehabilitation Research to explore "multimodal rehabilitation approaches that promote plasticity and sensorimotor function". Results from this study will provide the preliminary evidence necessary to design and implement a large, multi-center RCT to test the efficacy of NICU-based rehabilitation programs to improve the motor outcomes of infants born preterm.

General Information

Protocol title: Neonatal Rehabilitation Program for premature infants at risk for cerebral palsy
Protocol number: R03HD097727 - 01
FOA: PAR18-211 NCMRR Early Career Research Award (R03 clinical trial optional)
Eunice Kennedy Shriver National Institute of Child Health & Human Development

Rationale & Background Information

Significance: CP is an umbrella term used to describe a spectrum of disorders related to movement and motor abnormalities that are non-progressive in nature. CP develops after injury to the developing fetal or infant brain.[1] However, in some cases the underlying pathology remains unclear without a history of periventricular leukomalacia, intraventricular hemorrhage, birth asphyxia or neonatal stroke.[1] The reported incidence and prevalence of CP has varied overtime but has not been mitigated by advances in medical care resulting in increased survival of premature and low birth weight infants. Premature infants are at increased risk of CP with the highest prevalence seen in those born at less than 28 weeks gestation.[2-3]

Magnetic resonance imaging (MRI) can predict CP with high probability in severe cases, however not for mild-to-moderate CP, resulting in delayed diagnosis and treatment.[4] As a result, the mean age for diagnosis of CP is 1-2 years of age.[1] As such, treatment algorithms are centered on supportive and corrective care and are typically reserved to pre-discharge and most often post NICU discharge time periods. The NeoRehab program aims to address this gap by introducing intervention early during the NICU stay.

Innovation:

The possibility of intervention in the NICU is attractive because the brain is highly plastic and actively developing. Interventions at this stage may have a profound disease modifying impact.[5-6] Several investigators have evaluated the impact of early intervention strategies on neurodevelopmental outcomes in preterm infants reporting a positive effect on behavioral problems, social-relatedness, and cognitive and language performance.[7]

Infant massage represents a form of environmental enrichment that has a positive impact on multiple important outcomes after preterm birth including: improved weight gain, decreased stress and improved neurodevelopmental outcomes.[8-16] Infant massage can be administered by NICU therapist (UVA has several therapists trained in infant massage) and the feasibility of infant massage by the mother is being actively investigated.[17]

Similarly, early PT in the NICU leads to multiple positive outcomes including: increased bone mineralization and reduced incidence of motor delays in very low birth weight infants.[18,19] Parent-administered PT has recently been shown to be feasible.[20] Results from a recent RCT indicate that a 10 minute intervention twice a day for 3 weeks, from 34 to 36 weeks' PMA resulted in improved motor performance at 37 weeks' PMA. The intervention was supervised by a PT and was primarily designed to promote postural control, head control, and midline orientation.[20]

Finally, studies have shown that interventions promoting the establishment of emotional connection between infant and mother, such as the Family Nurture Intervention (FNI) strategy, can positively impact neurodevelopmental outcomes at 18 months.[7]The FNI targets infants 26-34 weeks PMA and aims to reduce the effects that abnormal sensory inputs in the NICU have on the developing brain.[21] The program aims to enhance the emotional connection between mothers and their premature infants.[7, 21] Nurture specialists met with mothers on average 6.4 hours per week over the course of the NICU stay and continued until discharge (35-38 weeks' PMA). Elements of the FNI include mother/infant calming sessions with scent cloth exchange, vocal soothing, eye contact, kangaroo care, and family-based support sessions. It can be implemented shortly after birth and incorporates multiple elements of routine NICU care, an important point for implementation

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Study goals and objectives

The goal of this project is to investigate the acceptability, feasibility and fidelity of an innovative NICU rehabilitation program that will include six multimodal, GA appropriate, parent-administered interventions (vocal soothing, scent exchange, comforting touch, kangaroo care, infant massage and physical therapy). We will also determine the effects of this program on short-term motor outcomes using the HINE, the GMA and the TIMP instruments in premature infants (≤32 week's gestation and/or ≤1500 grams birthweight).

AIM 1: Enroll 60 preterm infants (<32 weeks' gestation and/or ≤1500 grams) into a pilot RCT to evaluate the acceptability, feasibility (practicality) and fidelity (adherence, exposure and engagement) of a multimodal GA appropriate rehabilitation program during NICU hospitalization compared to standard of care. We will evaluate:

- Acceptability using recruitment, refusal, retention, and follow-up rates as well as weekly interviews with parental participants
- Feasibility (practicality) using direct observations and weekly interviews with parental participants
- Fidelity (adherence, exposure and engagement) using visitation data, activity logs, direct observations, and weekly interviews.

AIM 2: Examine the effect of a multimodal NICU-based rehabilitation program on short-term motor outcomes (general movements, cranial nerves, posture, movements, tone, and reflexes) of premature infants at risk for CP at discharge from the NICU and at 3 months PMA. We hypothesize that this type of GA appropriate multimodal NICU-based rehabilitation program will positively impact short-term motor outcomes by normalizing general movements and improving TIMP and HINE scores.

STUDY DESIGN

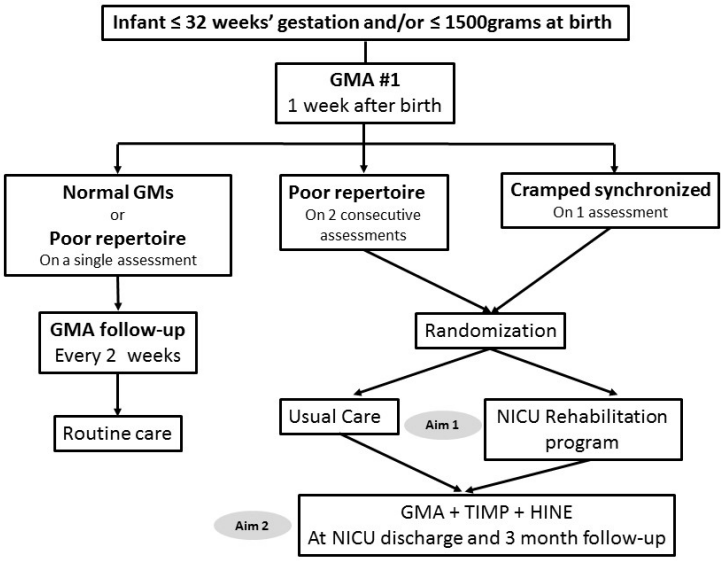
Methodology: The design will be a RCT at a single site academic NICU-UVA Hospital in Charlottesville Virginia. Randomization will be stratified by birth weight (< 1000 grams and 1000-1500 grams) using a randomly permuted block design with random block sizes of 2 and 4. The intervention group will receive a novel multisensory, multimodal rehabilitative program, which will incorporate elements from the FNI program (scent exchange, touch, vocal soothing) as well as infant massage and parent-administered physical therapy. The intervention will be adjusted to take into account the infant's developmental stage and physiologic stability (See **Table 1**). Additionally, the intervention focuses heavily on interventions the parent can provide.

Inclusion and exclusion criteria:
Infants will be eligible for this study if they meet the following criteria:

- GA at birth: ≤32 weeks gestation and/or birthweight ≤1500 grams
- Infants 7 days or older
- Parental ability to perform the interventions or identified designated surrogate (e.g. grandparent)
- Abnormal writhing GMs defined by the presence of a poor repertoire pattern on 2 consecutive weeks or the presence of a cramped-synchronized pattern on any assessment (see **Figure 1**)

Infants will be excluded from the study if they are clinically unstable (requiring high frequency mechanical ventilation, vasopressor support, need for continuous intravenous pain or sedation medication), if their parents do not speak English or if parental participation is hindered (e.g. incarceration or work/personal related issues).

Figure 1: Intervention algorithm



Intervention (n=30): Parents will be provided oral as well as written (Flip book) and illustrated information about the interventions. Study team members will assist with demonstrating appropriate technique for applying interventions and will use the teach-back method to ensure comprehension and understanding. Interventions will be developmentally tailored to the infant's GA (Table 1) as follows:

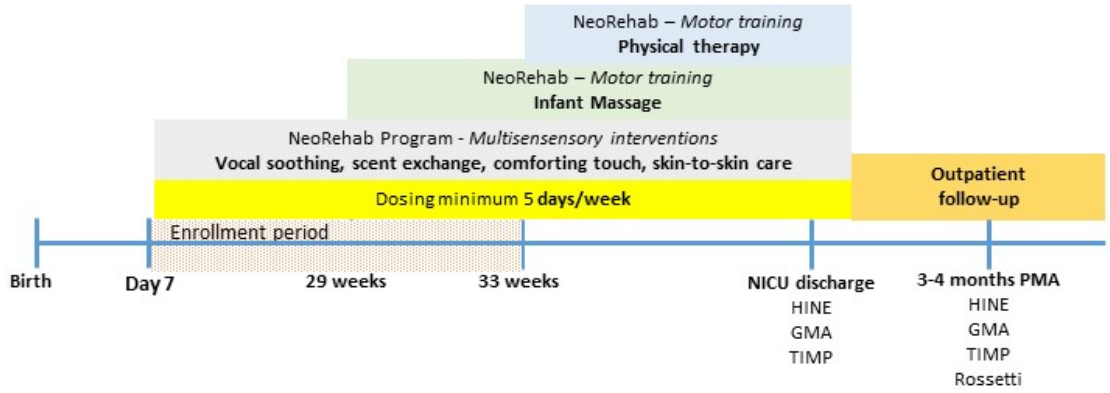
1. Modified FNI portion of the bundle includes:
    a. Vocal soothing: mothers will be instructed to express their feelings to their infant in their native language using varying intonations
    b. Scent exchange: on initial visit, mothers will receive 2 cloths, 1 to place in her bra and 1 to place under her infant's head. Cloths are subsequently exchanged at each visit.
    c. Comforting touch: mothers will be instructed to use gentle but firm and sustained touch by placing the infant's arms on the chest and placing their hand on top. The other hand will be used to gently contain the infants' feet, lightly drawing the knees towards the chest.
    d. Mother-Kangaroo-Care plus: kangaroo care will be combined with gentle touch, vocal soothing and eye contact as described above.
2- Infant massage: mothers will be taught moderate pressure massage by PT
3- Parent-administered PT: 10 minutes interventions promoting postural and head control as well as midline orientation will be conducted by the mother is recommended starting at 33 weeks' PMA. The intervention will be monitored by a physical therapist for 3 consecutive sessions and weekly thereafter.

Mothers/Fathers whose infants are randomized to the intervention group will be encouraged to be at the bedside and provide the GA appropriate interventions once per day, 5 days per week (5/7).

Table 1: Developmental-Guided NICU based rehabilitation program

	Postmentrual Age (completed weeks)				
Interventions	**23-25**	**26-28**	**29-32**	**33-36**	**≥ 37**
Vocal soothing	———	———	———	———	———
Scent exchange	———	———	———	———	———
Comforting touch	———	———	———	———	———
Kangaroo care plus		———	———	———	———
Infant massage			- - - - - - - - - -	———	———
Parent-administered PT				———	———

Standard of care (control group) (n=30): Parents of infants randomized to standard care will continue to be encouraged to touch, hold, and talk to their infants. They are also encouraged to perform kangaroo care based on unit guidelines. All infants in standard care will have a routine physical therapy consult at 28 weeks gestation. The infants will continue to be followed 2-3 times per week for 10-30 minutes per session by PT until discharge from hospitalization. Social work actively engages with parents of infants admitted to the NICU which will include the intervention and standard of care group. Social work provides ongoing parental support and strives to alleviate barriers to visitation. At time of discharge standard care will resume for both groups, which includes a referral to early intervention and a NICU follow up appointment with developmental pediatrics at 3 months PMA. Below is the study schedule.



Self-report activity logs (separately uploaded documents) will be used to monitor the fidelity of the program. Both groups will fill out the log and document what aspects of the program were performed, the date, and duration of the intervention. Weekly interviews will be conducted with parental participants to evaluate the acceptability (satisfaction), feasibility (practicality) and fidelity (engagement) of the program. Weekly interviews will be done at the bedside with parental participants and a research team member to discuss any challenges or barrier to applying the recommended evidence based practice interventions. Examples of interview questions are 1) How are things going? 2) Do you have any questions about the interventions? 3) Are there things that are preventing you from doing the interventions? Additionally, research team members will perform random direct observations of intervention application to further evaluate feasibility and fidelity.

Safety considerations

Risk of loss of confidentiality and privacy
Risks related to the Maternal/Designee Activities with Baby:
Rare but serious:

- During Kangaroo Care there is a rare risk that infant may fall or that a tube or line may be dislodged.
- Injury to muscles or bones due to improperly applied infant massage

General: Infants in the NICU and family members are encouraged to participate in developmentally appropriate activities. However, these activities are not applied in a systematic fashion. The intervention group is at no greater risk than the standard care group as interventions evidence based and has been applied in the NICU setting.

Adverse events are monitored for the entirety of the study.

Follow up

Interventions will be completed upon discharge from the NICU. Usual care resumes for both groups at discharge. Outpatient follow up for secondary developmental outcomes will occur at 3-4 month follow up appointment (see study schedule).

Data management and statistical analysis

IRB approval and informed consent will be obtained prior to the start of the study. Video recorded GMA is standard of care in the NICU for neonates born ≤32 week's gestation and/or ≤1500 grams birthweight. Videos will be reviewed and scored independently by at least 2 of the study investigators. Videos will be scored with only the PMA information available to the investigator at the time of review. Inter-rater and intra-rater agreement will be assessed using Cohen's kappa (kappa) and percentage agreement. In case of

disagreement, the videos will be reviewed by all study members trained in the GMA and a consensus will be obtained.

The UVA NICU admits an average of 112 very low birth weight infants every year among which 83 are born at 32 weeks' gestation or less. We anticipate that, in one year of accrual, there will be approximately 120 infants <32 weeks gestation and/or ≤1500g birth weight. Based on a preliminary assessment of children in the NICU, we expect that 80% of these children will be eligible for the study. Recruitment acceptance rates of previous studies conducted in our NICU range from 30-50% for intervention studies and 80-90% for noninvasive studies. Using an acceptance rate of 80% yields an expected accrual of 70 patients per year. Allowing for 10% dropout, accrual of 33 patients per group (power calculation below) can be completed in 1 year.

Quantitative data will be analyzed using descriptive statistics and content analysis will be performed for qualitative responses. Quantitative data will be analyzed using the newest version of SPSS. Due to the exploratory purpose of the specific aim, descriptive statistics will be computed for all quantitative variables (demographic characteristics, recruitment, refusal, retention, follow up rates, % completion of self-report log and number of visitations per unit log). Frequencies and rates will be calculated for categorical variables and means and standard deviations will be calculated for continuous variables.

Qualitative analysis will included semi-structured interviews with adult participants as well as direct observations using qualitative description. Qualitative descriptive analysis will provide a comprehensive evaluation of the NICU multimodal rehabilitation program. The textual data from the interviews and observation notes will be analyzed by (1) immersion in the data (2) followed by line by line analysis and data reduction of the textual data through inductive open coding and constant comparative analysis.[36-37] Tentative categories will be listed with each line of data and identified by "nodes" in the Dedoose software. (3) After line-by-line analysis of the transcripts, categories ("nodes") will be grouped together to form tentative themes.

Repeated measures models will be used to compare HINE and TIMP total scores at the time of discharge and at 3 months PMA between newborns in the standard care group and in the intervention group (NEO rehab program). F-tests based on contrasts will be used to make comparisons at the two specific time points. To approximate the power of the F-test for comparing the groups with respect to the 3-month HINE scores, the results in Romeo et al.(2008) were used. Their study showed that across CP diagnoses, the average 3 –month HINE score was approximately 40 with an estimated standard deviation of 8.8. A score of below 40 is associated with the GMFCS IV and V levels while a score of 40-60 is associated GMFCS levels I and II at 3 months of age. A score ≥ 73 is optimal. With 30 subjects per group, the two-sample t-test has 80% power, with a 2-sided significance level of 5% when the effect of the intervention is to increase HINE scores by 6.5 points. Allowing for 10% dropout, 33 patients per group are required. Similar analyses will be used for the TIMP scores as well as subscales of the HINE. For the GMA assessments, we will tabulate the proportion of children in each group classified as having poor repertoire, cramped/synchronized or chaotic movement abnormalities at each of the follow-up times. Markov models will be used to assess how the intervention affects the proportions of children transitioning between classifications. For all of the endpoints; this study will provide estimates of variation useful for planning a larger study of the rehabilitation program. Our primary analysis will be done as intention-to-treat.

Quality assurance

Human Subject Research Institutional Review Board approved study
DSMB not required for this project

Expected outcomes of the study

Acceptability, feasibility and fidelity will be evaluated to ensure that the study design is sound for a future full-scale intervention study, Table 2.

- Acceptability using recruitment, refusal, retention, and follow up rates as well as weekly interviews with parental participants
- Feasibility (practicality) using direct observations and weekly interviews with parental participants
- Fidelity (adherence, exposure and engagement) using visitation data, activity logs, direct observations, and weekly interviews

Table 2: Primary outcomes

Variable	Concept	Domain	Metrics
Acceptability	Satisfaction	Correct, consistent and continuous use of the program	1. ≥75% Recruitment rates 2. <10 % Refusal rates 3. 75% Retention rates 4. 90% Follow-up rates 5. Weekly interviews with parental participants
Feasibility	Practicality	Adequacy of the logistics a) determining the capability of carrying out the program as planned b) identifying difficulties in applying any aspect of the program	1. Direct observations 2. Weekly interview the parental participants
Fidelity	Adherence	a) pro portion of the program content, b)methods and c) activities	1.>75% Completion of self-report activity log to be completed by parental participant 3.Direct observations by research team member
Fidelity	Exposure	a) number of sessions, b) attendance, c)frequency and d) duration	1. Self-report activity log to be completed by parental participant 3.Direct observations by research team member 4. Administrative data (NICU visitation log)
Fidelity	Engagement	Participation in the program	1. Weekly interviews conducted by research team member with parental participants 2. Administrative data (NICU visitation log) 3. >75% Completeness of the activity logs

The short-term impact of these combined interventions on motor function will be assessed using the HINE, theGMA and the TIMP. These instruments will be administered at time of discharge from the NICU and at 3 months PMA. These instruments used in combination are recommended to be administered to infants before 5 months PMA and provide the most predictive of risk for CP. Instruments will be administered by certified providers and/or therapists. Additionally, demographic characteristics of the sample will be collected using the medical record and include: gender, ethnicity, race, gestational age at birth, birth weight and head circumference, primary diagnosis, neurologic comorbidities, medication management of neurologic comorbidities and neonatal abstinence syndrome, NICU length of stay,

feeding method upon discharge, discharge head circumference, geographical region, and disposition (death or discharge home).

Table 3: Short term developmental outcomes

Instrument	Measurement	Age	Interval
HINE	26 items used to assess cranial nerve function, posture, quality and quantity of movements, muscle tone, and reflexes and reactions). Each item is scored individually 0-3 with a sum score of all individuals ranging from 0-78. Lower the score the poorer the motor function. The HINE allows for identification of early signs of CP and individual items have demonstrated predictive value of motor outcome. Sensitivity 90% for prediction of motor outcome.	2 and 24 months of age	At time of discharge and 3 months PMA
GMA	Writhing stage 1) normal 2) poor repertoire- monotonous and lack complexity 3) cramped-synchronized- appear rigid and are not smooth or fluent in character. 4) chaotic -characterized by abrupt, large amplitude movements involving all limbs. Fidgety stage 1)normal 2) abnormal fidgety movements-absent or abnormal (exaggerated). Cramped-synchronized followed by absent fidgety pattern, have a 98% sensitivity and specificity for prediction of CP	Writing movements birth-9 weeks Fidgety movements 9-20 weeks	Every 2 weeks during hospitalization and 3 months PMA
TIMP	28 observed items of spontaneous movements and 31 elicited items that assess the child's motor responses scored 0-6. The lower the score the poorer the motor function. The test is sensitive to age-related changes in motor performance (r =0 .83).	32 weeks to 4 months post term	At time of discharge and 3 months PMA

Dissemination of results and publication policy

Presentations at National Meetings: We plan to present our findings at national scientific meetings annually.

Publication in Journals: We aim to publish all data and results generated from this proposal in conference abstracts and manuscripts. We will aim for high impact open access journals with wide readership. All publications will be available through PubMed Central. [http://www.ncbi.nlm.nih.gov/pmc]

Communication with local authorities: Not applicable in this grant

Sharing Model Organisms: Not applicable in this grant.

Genome Wide Association Studies: Not application in this grant

Duration of the project

Project period begin date 4/4/2019
Project period end date 3/31/2022

Study timeline- 24 months

Months 1-2	Finalize IRB approval
Months 2-14	Recruitment and data collection
Months 14-18	Data management and analysis
Months 18-24	Dissemination
Months 18-24	Grant preparation for next step- R01 to include long term motor outcomes

Problems anticipated/encountered

Due to COVID a 1 year no cost extension was obtained

1. The concept of hospital-based NICU multi-modal rehabilitation is innovative and may not be viewed as "traditional rehabilitation." However, this model of rehabilitation requires a different approach and consideration given the developmental age of the subjects and the unique NICU setting.
2. To ensure patients are not lost to follow up, complimentary phone calls will be provided prior to their scheduled appointment. If transportation issues arise, social work is available to assist. In the future, home visits to perform these developmental assessments maybe more accepted then an outpatient clinic follow up appointment.
3. The primary end point of this study is feasibility. However, the research team is particularly interested in the impact of these interventions on developmental outcomes. While short term outcomes maybe demonstrate significant differences between treatment arm, short term and long term outcomes will need to be further evaluated in subsequent studies and may incorporate other markers of health.

Ethics

HSR IRB approval (# 21502) was obtained prior to initiating any study procedures.

This proposed research will in human subject research. Institutional Review Board will be obtained. Informed consent will be obtained (supplemental attachment).

This proposal seeks to investigate the acceptability, feasibility, fidelity of a neonatal intensive care unit (NICU) rehabilitation program that will consist of gestational appropriate interventions. Additionally, we will determine the effects of short term motor outcomes of the program in premature infants identified to be at risk for cerebral palsy (CP). Will seek to enroll 60 participants.

Recruitment and Retention Strategies: Our study team has existing relationships with the academic NICU. The PI is a member of the Neuro NICU team. Study participants will have the opportunity to learn about the research and ask questions and make suggestions. The study participants will be meeting with a member of the research team weekly. Recruitment and retention rates will be monitors and considered an outcome measure to determine acceptability of the program.

Recruitment and Informed Consent

Participants will be recruited after IRB approval at the University of Virginia has been obtained. Patients will be recruited from the NICU after meeting the outlined inclusion/exclusion criteria. Informed consent will be obtained for all participants. There will be opportunities to ask questions, and are informed that they may withdraw from any part of the study at any time. Randomization will not occur until consent is obtained.

Protections Again Risk

Participants enrolled in the studies are told of the risks, benefits and alternatives before the studies start and are able to withdraw at any time. Risks are minimal and every effort is made to explain things clearly to participants and allow the participants to ask questions. Researchers completing analyses will have only de-identified data. All data are kept locked and secure. Names are not used on forms.

Potential Benefits of the Proposed Research to Human Subjects

We anticipate that the NICU-based intervention program will be well accepted and feasible. Additionally we hypothesize that the intervention will result in improved short term motor outcomes. Information gained may help improve care of infants at risk for CP.

Informed consent forms (uploaded as a supplement document)