FOLLOW-UP STUDY

Follow-up of High Risk Infants

Protocol

NICHD Neonatal Research Network

Original Protocol: August 23, 2007
Revision: September 24, 2007 (ELBW language removed)
Revision: July 01, 2012 (FU window change to 22-26 months)
Revision: September 10, 2013 (Replaced BITSEA with CBCL)
Revision: June 28, 2023 (Replaced Bayley III with Bayley 4)

ABSTRACT

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) initiated the Neonatal Research Network (NRN) in 1986. In 1993 a follow-up Study was added; the purpose is to collect data related to growth and physical, neurological, behavior and neurodevelopmental status at a pre-defined corrected age. Initially the study examined 18 + 4 month corrected age outcomes of infants who were registered in the Network's Generic Database and who weighed between 401 and 1000 grams at birth. In 2008, the inclusion criteria for the Study were expanded to include infants who were born at less than 27 weeks of gestational age and all babies enrolled in a randomized trial or an approved observational study. In 2012, the timing of the assessment was changed from 18-22 months corrected age to 22-26 months corrected age for babies born on or after July 1, 2012 and those enrolled in specific clinical trials. For infants seen for the Follow-Up Study at 22-26 months corrected age, the Brief Infant Toddler Social Emotional Assessment (BITSEA) was replaced with the Child Behavior Checklist [CBCL (ages 1.5-5 yrs)]. Eligible infants born before July 1, 2012 were evaluated at 18-22 months corrected age and the BITSEA was administered. The NRN 2023-2030 cycle includes 15 clinical centers and three collaborating centers across the United States that collect data on perinatal/neonatal outcomes. Protocol development, data management, and analysis are the responsibility of the Data Coordinating Center located at RTI International.

INTRODUCTION

The NICHD initiated the NRN to conduct multi-center clinical trials and observational studies in an effort to reduce infant morbidity and mortality and to improve the health of low birth weight and premature infants. The Network was created in large part because many of the treatment and management strategies that were in place in 1986 had become standards without being properly evaluated. The development of a uniform approach to collect follow-up information in the extremely low birth weight (ELBW) infant (less than 1000 grams) and < 27 weeks gestation is an essential component of the NICHD NRN mission. Only by establishing a long-term outcome database can there be an evaluation of the risk and cost benefit of new technologies introduced in neonatal intensive care units. In addition, outcome data can be analyzed and used for assessment of quality of care, center differences, and/or time periods. The relationships among antenatal characteristics, neonatal characteristics and outcomes can also be evaluated. Data can be utilized for program initiatives by health care providers, policy makers, and health care planners.

Overall, the Follow-Up Study addresses outcomes in early childhood. In addition, follow up at later ages has been a component of several large clinical trials including the Glutamine, Hypothermia, SUPPORT Neuroimaging and Neurodevelopmental Outcomes, Hydrocortisone for BPD (HYBRiD), and Transfusion of Prematures (TOP 5) cohorts.

During the genesis of the Follow-Up study in 1995, study protocols, a study manual and forms were developed and a uniform assessment battery was identified. The follow-up protocol has been modified and updated on several occasions. The infrastructure includes a core of follow-up principal investigators, psychologists, and study coordinators, the development of training protocols for examiners, the establishment of inter-rater reliability, and data collection methods for follow-up assessment.

PURPOSE OF STUDY

The purpose of the NRN Follow-Up Study is to track and successfully evaluate babies who meet pre-defined inclusion criteria:

- Enrolled in the NRN Generic Database (GDB) born <27+0/7 weeks estimated gestational age (EGA) OR
- Enrolled in a randomized trial or approved observational study with developmental follow-up as a predefined primary or secondary outcome

BACKGROUND AND SIGNIFICANCE IN RELATION TO HUMAN HEALTH

Modern neonatal intensive care has had major therapeutic advances which resulted in a dramatic improvement in survival of extremely low birth weight infants (ELBW) (< 1000 grams).[1] [2-3] This has been most significant among extraordinarily preterm infants(i.e., <24 weeks EGA).[4-6] Compared to more mature infants, these infants have a higher incidence of neonatal morbidities,[7-11] complex chronic medical conditions (respiratory, gastrointestinal, feeding, growth failure), and poor neurodevelopmental outcome (neurologic, sensory, developmental, and behavioral).[8-14] Follow-up of these infants is clearly indicated to ensure that appropriate supports, resources, and interventions are in place for both the infants and their families

Limitations have been identified in follow-up studies of the extremely preterm population. These include:

- Lack of uniformity in outcome measures and study definitions,
- Variable age at time of outcome assessment,
- Inadequately defined or described study populations,
- Lack of appropriate comparison control groups,
- Failure to consider other sibling, family, or environmental factors which may affect outcome independent of prematurity and medical complications,
- Failure to quantify severity of illness in perinatal/neonatal periods,
- Lack of adequate socio-economic and other health characteristics data collection,
- Lack of consistency in correction for prematurity, and
- Lack of accurate gestational age assessment.

Because of the considerable resources needed in the care of extremely preterm infants, it is imperative that accurate outcome data are collected. However, evaluation of outcome is complex and requires attention to several major areas. First, it is clear that outcome assessment must be performed early enough to directly reflect the perinatal-neonatal intensive care experienced by these infants, but at an age when accurate assessment of major neurodevelopmental outcome is achieved. This entails the use of standardized and uniform testing instruments performed on a large population of surviving infants. Second, the correlation of specific neonatal and perinatal morbidities with developmental outcome should be evaluated. Third, the relationship of family resources and home environment to neurodevelopmental outcome must be assessed. Finally, the perceptions of the child's caretakers should be evaluated and compared to objective measures of child behavior and development as assessed by developmental experts.

Expertise in neurologic, developmental, behavioral, and growth evaluation and coordination is present at each of the participating NRN centers, and all have participated in the development of the follow-up program procedures. Follow-up in early childhood

provides essential data on a continuous basis enabling the effectiveness of perinatal and neonatal intensive care to be monitored as it changes over the years. Follow-up in later childhood is essential to ultimately document the true functional outcomes of these and other high risk infants. Having a uniform protocol in place at each center has enabled the Network to support additional studies of particular importance to investigators at all or several of the NRN centers. Other high risk populations of term or near term infants involved in intervention trials are easily followed by consistent and uniform assessment as well. Follow-up protocols are applied to patients enrolled in the primary trials as well as in ancillary studies. The ability to perform consistent outcome assessment enhances the research productivity of participating centers by facilitating the performance of ancillary studies of interest to specific centers. The benefits of establishing and sustaining the follow-up program are deemed worthy of the investment of the necessary resources and personnel.

The primary goal of this follow-up protocol is the ongoing assessment of physical, nutritional and neurodevelopmental outcome of the highest risk newborn intensive care population in the United States. Only through a multicenter cooperative effort can adequate numbers of infants be evaluated for meaningful and timely determination of outcome which can be related to current newborn intensive care practices. In order to accomplish such a cooperative effort, the protocol and instruments employed must:

- be relatively simple, achievable in a reasonable period of time,
- encompass major areas of physical and neurodevelopmental maturation,
- be reproducible within and between centers and investigators,
- be able to be administered by a variety of professional staff, and
- be standardized for the age at which evaluation will be performed.

The protocol and instruments selected have a theoretical rationale but also are pragmatically driven. The battery of tests is a balance between the ideal, comprehensive, and detailed assessment and what logistically can be accomplished given the constraints of the multicenter design and limited resources. Enumerated in the following sections are hypotheses and study objectives which derive from the ongoing collection of data on this population. The specific instruments which are employed are described with a brief description of the reason for their selection and the strengths as well as the limitations of these instruments. This protocol is intended to be the best comprehensive neurodevelopmental assessment within the time and cost restraints of the Network.

Control subjects are not obtainable outside of this group due to their uniqueness in fulfilling the inclusion criteria as GDB infants or infants enrolled in a NRN randomized trial or approved observational study. Moreover, recruiting and tracking a full term control cohort requires resources, both financial and personnel, beyond the resources allocated within the NRN.

SPECIFIC AIMS

The Follow-up Program of the NICHD NRN is a comprehensive study which examines the neurologic status, gross motor function, and developmental domains of cognitive, language and motor skills in a group of infants < 27 weeks gestation or in trials. Outcome assessments are performed in early childhood (based on best obstetrical estimate) to directly reflect the perinatal-

neonatal intensive care, and to provide an accurate assessment of major neurodevelopmental outcome.

HYPOTHESES

The following hypotheses have been identified for the Follow-up Study of infants < 27 weeks gestation:

1. Increased survival of infants in this population is associated with no increase in rate of neurodevelopmental morbidity.
2. Higher birth weight and/or gestational age of infants in this population is associated with higher percentage of neurodevelopmental outcome within the normal range and lower percentage of neurodevelopmental impairment.
3. Improved neurodevelopmental outcome is associated with higher socio-economic status (SES) and lower neonatal morbidity.
4. Post hospital discharge mortality increases with decreasing SES.
5. Lower birth weight and/or gestational age is associated with higher percentage of growth failure.
6. Instability of families of infants is associated with an increase in neurodevelopmental morbidity.
7. Utilization of special services is directly related to neurodevelopmental outcomes.
8. Prenatal and postnatal condition, care and interventions impact the neurodevelopmental outcomes.
9. Post discharge (post hospital) interventions have a positive impact on the neurodevelopmental outcomes and well-being.

STUDY OBJECTIVES

1. To track and successfully evaluate babies enrolled into the NICHD Neonatal Research Network Generic Data Base registry with a gestation < 27 weeks and babies enrolled in a randomized trial or previously approved observational study.
2. To characterize development of the study population by standardized methods in the areas of motor skills, cognitive skills, neurologic status, language, and behavior.
3. To determine mortality and the prevalence of specific medical morbidities.
4. To characterize growth outcome and its relationship to neurodevelopmental outcome.
5. To identify the socio-economic status of the families and its relationship to developmental outcome.
6. To identify significant family stress and its relationship to family integrity as well as compliance with medical and developmental care.
7. To assess the utilization of special support services and early intervention programs
8. To examine the relationship between a need for intervention based on study assessment (developmental, functional, and medical outcomes) and the percent of children receiving intervention services.

METHODOLOGY AND PROCEDURES

Study Design

The NRN **Generic Data Base (GDB)** is a repository of perinatal/neonatal outcome data collected on all infants born at one of the participating Centers and who meet inclusion criteria. A follow-up assessment, which includes all aspects of growth and development, will be undertaken for all infants born < 27+0/7 weeks gestation at 22-26 months corrected age based on ***best OB estimate***. (If the gestational age by best OB estimate is missing, the gestational age by Ballard should be used).

Selection of Participants and Recruitment of Study Population
The Follow-up Study includes infants enrolled in:

- the GDB who are born <27+0/7 weeks EGA OR
- a randomized trial or approved observational study with developmental follow-up as a predefined primary or secondary outcome.

The NRN 2023-2030 cycle includes 15 clinical centers and three collaborating centers across the United States. In accordance with NICHD's 2020 Strategic plan which includes promoting greater availability of infrastructure and to facilitate greater involvement of diverse populations in clinical trials, the NRN implemented the Open Network in April 2023 to ensure that NRN trials can be completed expeditiously within a reasonable timeframe and with inclusion of diverse populations. As such, the number of clinical centers participating in the NRN Follow-up Study is dependent upon the number of institutions participating with the Network in specific protocols. Infants that meet inclusion criteria have a Discharge SES Data Form (NF01) completed at the time of their discharge. Informed Consent procedures are conducted for all subjects in accordance with practices at their institution prior to the follow-up evaluation. Tracking information is collected to enable study staff to keep in contact with the family until the time of the follow-up visit.

STUDY PROCEDURES

Description of the Visit in Early Childhood
The follow-up visit includes the following assessments, each with its accompanying data forms.

- Demographics (NF03)
- Medical history including neurosensory outcomes (NF04)
- Physical and neurological examination (NF05)
- Neurodevelopmental and behavioral assessment with the Bayley Scales of Infant Development-4 (NF09B4)
- Social/behavioral development with the Child Behavior Checklist [CBCL (ages 1.5-5 yrs)]

Tracking information will be updated at the follow-up visit for potential future visits.

Certification of examiners
There are procedures for annual recertification for Network protocol assessments for the neurological examiners and the Psychologists.

Neurologic examiners The process includes the submission of an annual video along with appropriate Network study forms completed by the site examiner performing the complete neurologic exam to a Network gold standard examiner. Feedback is received. A second component for achieving inter-rater reliability includes participating in an annual workshop at which time 4-6 videos of neurologic exams (scored by the examiner on Network forms prior to the workshop) are reviewed by participants and discussed for consensus.

Psychologist/Psychometrist examiners This process includes the submission to a Network gold standard examiner of an annual video along with appropriate Network study forms completed by the site examiner performing the complete Bayley exam. Feedback is received. Workshops are held as needed for training and certification when introducing new tests for Network protocols.

Assessment Battery

The data collection process has been designed to eliminate subjective answers as much as possible and to provide objective and quantitative information. A special effort has been made to develop an assessment battery which minimizes inter-center variability, assure uniformity in testing, and consistency in data collection.

Demographics (Forms NF01, NF03)
Numerous studies have demonstrated the importance of family factors and the interaction between family factors and child characteristics as they relate to developmental and behavioral outcome. Socioeconomic status (SES) characteristics of the family have been shown to be predictive of outcome with increasing age. [14] In addition, more recent work has shown that characteristics of the family and home environment are significant predictors of outcome.[15-16] The demographic variables which have been chosen are based on prior studies confirming the importance of these variables, and the diversity within and among centers. These variables will be analyzed for their potential relationship to the study's outcomes.

Medical History (Forms NF04, NF04A)
This section is designed to review problems at hospital discharge, resolution of those problems, new problems since discharge, and resolution or persistence of these problems. The Medical History Form is designed to identify major morbidity, severity of medical conditions and the child's functional characteristics.

a. Major morbidity
The medical history questions have been designed to identify major morbidities and the frequency of morbidities. For example, "Does the child have a history of seizures? If so, how often?" The medical history questions collect information on how many times the child has been re-hospitalized since initial discharge as well as the diagnoses for each hospitalization. Whether the child has had surgeries will also be examined.

b. Severity of medical conditions
Grading conditions as mild, moderate or severe can result in ambiguity and may lack uniformity when done at multiple sites. To alleviate this problem, questions regarding the severity of conditions are explicit and focus on quantitative items such as, "Is the child currently using: Oxygen? Ventilator? Has the child had seizures? What

medications have been prescribed? What equipment is in use?" The use of medications and equipment will also reflect the duration and/or persistence of severity of illnesses. Functional characteristics other than neurological findings have been designed to identify primarily feeding and motor functioning. Responses will identify the level of care that is required, for example, "How does your child eat?" The responses range from normal self-feeding through choices leading to a gastrostomy tube.

Physical and Neurological Examination (Form NF05)
A physical and neurological examination will be conducted at the follow-up visit. The physical examination will include weight, length, and occipital-frontal circumference (OFC) measurements. These data will allow for follow-up of early growth parameters.

Traditional developmental tests identify certain cognitive and intellectual developmental problems but do not include a neurological examination and therefore do not identify neurological deficits. Thus, a standardized neurological examination to identify neurological abnormalities and functional gross motor skills is included and adapted from the standardized recording of central motor deficit as described by Amiel-Tison and Stewart.[17] The examination is intended for international use and describes functional gross motor skills in an objective manner without need for extensive judgment by the clinical examiner. Each area of the body (head and neck, trunk, lower limbs, and upper limbs) is divided into four functional and sequential skill levels. Neurologic examination also involves the description of muscle tone and movement with the child at rest and description of muscle tone and movement with excitement or goal directed movement. Severity of hypotonicity and hypertonicity, including identification of contractures, adductor spasm, and clonus, are quantified. The neurologic examination also includes evaluation of gross characteristics of oral motor skill development.

Sensory deficits are identified through specific questions concerning vision and hearing. For vision, the questions begin broad-based and become specific, identifying the need for corrective lenses, presence of strabismus, and partial or complete blindness. The severity of hearing deficit (if any) will be specified and characterized functionally as requirement of a hearing aid, unilateral or bilateral deafness, etc. These sensory parameters are essential in follow-up to determine major morbidities and severity of conditions as well as characterize functional use for development and outcome. In addition, these measures will allow correlation of outcome with early assessment of retinopathy and auditory brainstem testing performed during the initial hospitalization.

Major abnormal findings discovered on examination will be noted. These findings will not be itemized in a traditional physical examination format, but listed as a diagnosis or as findings of the neurologic examination. The neurological findings will be summarized and classified into neurological syndromes/diagnoses. In conjunction with the developmental test, they will provide a complete picture of the child's current neurosensory as well as developmental status. Neurological and motor disorders are listed and will be identified by the physician examining the patient. Sensory deficit will be identified by the examining team and are only noted as present or absent in the Diagnostic section (Form NF05-C-9).

The Gross Motor Function Classification system developed by Palisano et al.[17-18] is used to determine the level of gross motor function of infants at the follow-up visit. The Palisano et al. algorithm focuses on children's functional achievements rather than on their limitations starting with normal function and progressing to increasing levels of functional limitations. Distinctions between levels of gross motor function are based on functional limitations, the need for assistive technology including mobility devices (such as walkers and wheeled mobility), and to a much lesser extent the quality of movements. Level I represents the continuum of children with neuromotor impairments whose functional limitations are less than what is typically associated with cerebral palsy, or who have CP of minimal severity (such as "functional" children with hemi-syndromes). The distinction between levels I and II, therefore, are not as pronounced as the distinctions between other levels, particularly for infants who are 1 to 2 years of age. Assistive mobility devices which may be considered in distinguishing between levels II and III in older children are generally not used in children who are under 2 years of age.

Bayley Scales of Infant Development -Fourth Edition [19-20] (Form NF09B4)
The Bayley Scales have had a long and productive history both clinically and in research and much valuable data has been gathered relevant to child development using these scales. The Bayley-4 is appropriate for children aged 1-42 months. Assessment requires approximately 90-120 minutes for completion. With the caregiver present, items are administered directly to children by an examiner who has been trained and certified in the uses of these tests. Use of the Bayley for this study includes assessments of cognitive, language (receptive and expressive) and motor (fine and gross motor) development. The Motor assessment was added in January 2010.

CBCL (Form NF16)
The Child Behavior Checklist [CBCL (ages 1.5-5 yrs)] is administered to parents and includes 99 items that describe specific kinds of behavioral, emotional, and social problems that characterize preschool children. Items are scored on syndrome scales designated as Emotionally Reactive; Anxious/ Depressed; Somatic Complaints; Withdrawn; Attention Problems; Aggressive Behavior, and Sleep Problems. Items are also scored on DSM-oriented scales designated as Affective Problems, Anxiety Problems, Pervasive Developmental Problems, Attention Deficit/Hyperactivity Problems, and Oppositional Defiant Problems. The interview requires 10-20 minutes.

Lost to Follow-up (Forms NF12, NF19)
The Lost to Follow-up (LTFU) questionnaire (NF12) is completed for children not assessed at the Follow-up visit. It contains a caretaker questionnaire for cases in which the clinic is in contact with the family. The NF12 also contains a section for chart review or report from physician. In situations in which the NRN Center is still in contact with the family, the current edition of the **Ages and Stages Questionnaire (ASQ)** will be administered to caregivers of children not seen for the Follow-up visit as part of the LTFU package and the Summary Scores Form (NF19) completed.

Participant transfer between enrolling sites
When an enrolled participant(s) needs/want to follow up with a different study site, the original enrolling site will obtain and document verbal consent from the parent/legally authorized representative (LAR) to disclose her/his contact information to the new site. Written consent will not be required for this process. The new site will contact the parent/LAR to obtain site-specific informed consent and HIPAA before completing any

study-related activities at the new site. Alternatively, if desired by the parent/LAR, the enrolling site may provide the new site contact information to the parent/LAR and the parent/LAR can contact the new site themselves.

Visits at External Locations. In limited circumstances when families are unwilling/unable to travel to the study sites for their study visits, we will schedule these visits to occur in the subject's home or acceptable external site (such as a pediatrician's office). The same study personnel will conduct the visits at the external sites as would conduct the visits on site. All the same assessments will be completed at the external sites.

Extensive Travel Mechanism. The extensive travel mechanism will allow NRN Centers to receive additional funds per visit to cover **pre-approved** travel expenses (airline/train tickets, hotel, rental car, mileage reimbursement, etc.) for **trial** infants for:

1) Clinic staff to travel to conduct home visits for study patients that have moved far away (i.e., >200 miles), and are not close to another NRN Center, or
2) Families that have moved far away (i.e., >200 miles) to travel to the clinic for the visit.

Pre-authorization decisions will be made on a case-by-case basis, with no guaranteed approval. Only prospective requests (visits to be conducted) will be considered.

STUDY AND VISIT OVERVIEW

An overview of the Follow-up Study Procedures is given in Figure 1. A suggested order of procedures during the visit is given in Figure 2. Although the exact order of procedures at this visit cannot be predetermined as it depends on the appropriate state of the child, if possible, the Bayley Scales of Infant Development (BSID) should be administered early in the study visit before medical procedures or interviews. Best performance may be compromised if the child is tired, hungry, or upset. The caregiver should be present for this exam. Following the Bayley exam, the physical and neurological exam can be conducted. The caregiver should be present for these exams. The interviews should take place after the exams. The SES and Medical History should be conducted first, followed by the Child Behavior Checklist (CBCL).

Figure 1: Overview of the Follow-up Study Procedures

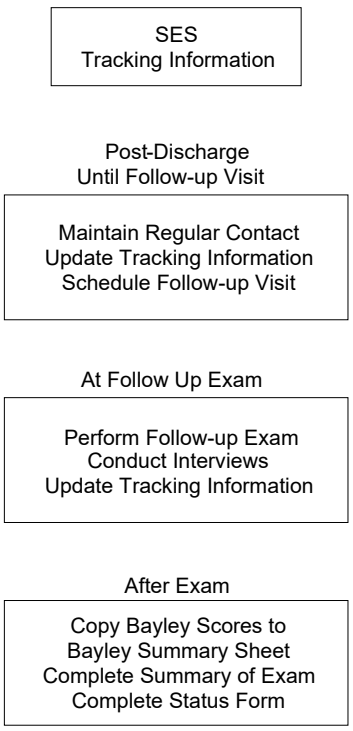
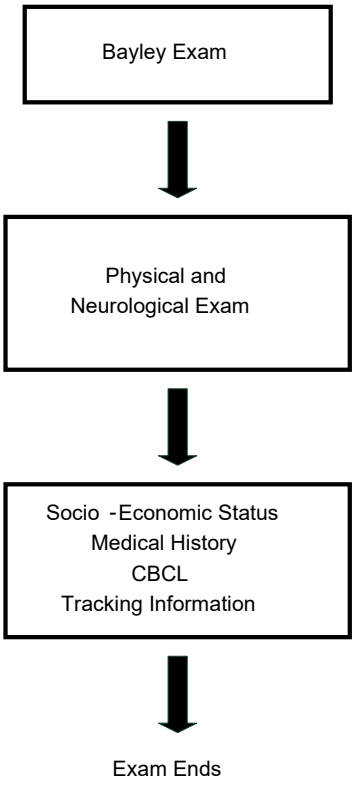


Figure 2: Overview of Follow-up Visit



DATA STORAGE AND MANAGEMENT

Each study subject has a data file including contact information and study forms that is housed at the NRN Center in which the infant is enrolled. All materials are stored in locked filing cabinet(s) at the NRN Centers as per IRB specifications. The NRN coordinators will collect required data using the designated study forms. Research personnel at each Center will then enter the collected data into the Network database, which is password protected. Patients are identified in the Network database by an assigned number which contains no individual identifiers. It is assigned by RTI and serves only to link the different data forms for an individual. No names, addresses, phone numbers, hospital numbers, social security numbers or other individual identifiers are contained in the RTI database and are not accessible by RTI staff. The link between the study assigned numbers and patient identifiers resides only at the hospital which enrolls the patient and is under the control of the study PI and the study coordinator at the hospital.

The NRN Data Coordinating Center (DCC), located at RTI International in Research Triangle Park, NC, is responsible for all aspects of statistical design and analysis as well as data management of the study. In concert with the NRN Steering Committee, the DCC is responsible for the protocol, manual, and forms development, and testing. The DCC, in collaboration with the subcommittee, conducts all statistical analyses and collaborates with the other Steering Committee members in the preparation of reports based on the study results.

SAMPLE SIZE

As of May 31, 2023, 93,824 infants have been enrolled in the NRN GDB since data collection began in 1987. The NRN Centers completed 20,477 follow-up visits between January 1, 1998 and May 31, 2023 with infants who met the inclusion criteria.

POTENTIAL BENEFITS

There are no anticipated direct benefits to participation in this study. However, there may be indirect benefit yielded by the administration of neurodevelopmental and physical/neurological assessment. Results of the neurodevelopmental examination and testing will be shared with the families and may be used for diagnosis, counseling and referral to developmentally appropriate services.

POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS

There are no known risks related to the assessments that will be completed for this observational research study. However, there may be some inconvenience related to traveling to the hospital for the follow-up visit.

A Data and Safety Monitoring Board is not necessary for this observational study since the protocol involves minimal risk to participants.

PROPOSED RISK/BENEFIT ANALYSIS

Based on the stated potential for benefit and the potential risks, we deem this study to meet the following designation:

⇒ Minimal risk without the potential for direct benefit to the subjects.

WITHDRAWALS
Any participant is permitted to withdraw from the study at any time without penalty.

PRIVACY AND CONFIDENTIALITY
As previously indicated in the section describing Data Storage and Management, measures have been taken to protect the privacy and confidentiality of study subjects. For example, all study materials are stored in locked filing cabinet(s) at the NRN Center in which the infant is enrolled as per IRB specifications. Research personnel at each Center will enter the collected data into the Network database, which is password protected. Patients are identified in the Network database by an assigned number which contains no individual identifiers. It is assigned by RTI and serves only to link the different data forms for an individual. No names, addresses, phone numbers, hospital numbers, social security numbers or other individual identifiers are contained in the RTI database and are not accessible by RTI staff. The link between the assigned study numbers and patient identifiers resides only at the hospital which enrolls the patient and is under the control of the study PI and the study coordinator at the hospital.

PAYMENT FOR STUDIES
Whether study subjects and their families receive payment for participation in this study is determined by each Network Center. Children are typically offered a developmentally appropriate toy or book for their participation and parents may be reimbursed for parking and travel expenses.

INFORMED CONSENT
Informed consent procedures are conducted for each subject in accordance with practices at their institution prior to the follow-up visit. Tracking information will be collected to enable study staff to keep in contact with the family until the time of the follow-up visit.

PARENTAL PERMISSION
Informed consent procedures are conducted in accordance with practices at each institution through their IRB's.

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