

Follow-up Care of High-Risk Infants

ABSTRACT. A workshop on the follow-up care of high-risk infants sponsored by the National Institute of Child Health and Human Development, National Institute of Neurologic Disorders and Stroke, and the Centers for Disease Control and Prevention was held June 19-20, 2002. There are currently no standardized guidelines for provision of follow-up services for high-risk infants in tertiary care centers despite the requirement for follow-up clinic experience in the 97 approved neonatal fellowship training programs in the United States and the increasing number of centers participating in multicenter networks. As the total number of survivors at risk for neurodevelopmental morbidities increases, many clinical research questions have surfaced that can only be answered by long-term follow-up studies. There is increasing awareness of the importance of long-term outcome in randomized, controlled trials, because perinatal interventions may dramatically alter later growth and development. There is also an increased recognition of the potential disconnect between perinatal outcomes and long-term outcomes. The administration of oxygen and postnatal steroids are prime examples of interventions that may have immediate positive effects but negative long-term effects. In addition, multicenter studies have identified significant center differences in the management and developmental outcome of high-risk infants. These findings led to the recognition of the need to improve standardization and comparability of methodology and data collection within and among centers and networks as a first step toward research to improve the long-term neurodevelopmental outcome of high-risk infants. The workshop participants met to define optimal methods to assess the outcome of high-risk infants, identify gaps in knowledge about the neurodevelopmental outcome of high-risk infants, and prioritize research efforts in response to these gaps. *Pediatrics* 2004;114:1377-1397.

ABBREVIATIONS. NICHD, National Institute of Child Health and Development; NICU, neonatal intensive care unit; RCT, randomized, controlled trial; ELBW, extremely low birth weight; VLBW, very low birth weight; CNS, central nervous system; MRI, magnetic resonance imaging; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; SES, socioeconomic status; MDI, Mental Development Index; PDI, Psychomotor Developmental Index; BSID-II, *Bayley Scales of Infants Development-II*; GMFCS, Gross Motor Function Classification System; ADHD, attention-deficit/hyperactivity disorder; NEPSY, Neuropsychological Test; BINS, Bayley Infant Neurodevelopmental Screener; LRO, Language Receptive Organization; LEO, Language Expressive Organization; CPT, Continuous Performance Test; CAT/CLAMS, Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale; TOVO, Test of Variables of Attention; CBCL, Child Behavior Check List; QOL, quality of life; CHQ, Child Health Questionnaire; HRQL, health-related quality of life.

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BACKGROUND

Advances in perinatal intensive care have been associated with improved survival of high-risk neonates but have not resulted in decreased morbidity. Small sample sizes, heterogeneity of cohorts and methodology, diversity of perinatal clinical practice, and the high cost of randomized, controlled trials (RCTs) and follow-up care have all contributed to the lack of rigorous data on the sequelae of preterm delivery and the therapies used to improve the long-term outcome of high-risk infants. In response to this need, a workshop on follow-up care of high-risk infants sponsored by the National Institute of Child Health and Development (NICHD) and the National Institute of Neurologic Diseases and Stroke was held in Bethesda, Maryland, on June 19 and 20, 2002. The goal of the workshop was to define optimal methods to assess the outcome of high-risk infants, identify gaps in knowledge about the neurodevelopmental outcome of high-risk infants, and prioritize research efforts in response to these gaps.

There are currently no standardized guidelines for provision of follow-up services for high-risk infants in tertiary care centers despite the requirement for follow-up clinic experience in the 97 approved neonatal fellowship training programs in the United States and the increasing number of centers participating in multicenter networks. As the total number of survivors at risk for neurodevelopmental morbidities increases, many clinical research questions have surfaced that can only be answered by long-term follow-up studies. There is increasing awareness of the importance of long-term outcome in RCTs, because perinatal interventions may dramatically alter later growth and development. There is also an increased recognition of the potential disconnect between perinatal outcomes and long-term outcomes. The administration of oxygen and postnatal steroids are prime examples of interventions that may have immediate positive effects but negative long-term effects.¹⁻⁴ In addition, multicenter studies have identified significant center differences in the management and developmental outcome of high-risk infants.⁵⁻⁸ These findings led to the recognition of the need to improve standardization and comparability of methodology and data collection within and among centers and networks as a first step toward research to improve the long-term neurodevelopmental outcome of high-risk infants.

OBJECTIVES OF THE WORKSHOP

1. To discuss the benefits of neonatal follow-up programs for nurseries providing neonatal intensive care unit (NICU) care.

2. To define who should be followed and what characteristics of premature infants and term infants are associated with an increased risk for neurodevelopmental morbidity.
3. To define the (1) the optimal ages of follow-up assessment and (2) the optimal assessment measures and to minimize barriers to assessment caused by motor, vision, or hearing impairments.
4. To discuss approaches to selection of controls and maintaining follow-up.
5. To describe alternative, less costly methods and approaches to assessment for the community physician.
6. Describe the challenges encountered in multi-center networks.
- 7A. To identify gaps in knowledge about assessment of neurodevelopmental outcome among high-risk infants and the mechanisms contributing to these outcomes.
- 7B. To further advance areas of investigation.
8. To propose future research questions.

OBJECTIVE 1: DETERMINE THE BENEFITS OF NEONATAL FOLLOW-UP PROGRAMS AT PERINATAL CENTERS

The 2 primary areas of responsibility for neonatal follow-up programs are surveillance and research.

Surveillance

The first step in surveillance is to establish a mechanism to systematically monitor the care of high-risk infants during their initial hospitalization as well as their general health and neurodevelopmental outcomes after discharge from the NICU. Surveillance is necessary for NICUs to (1) audit NICU interventions, (2) monitor important quality indicators for the individual NICU, (3) summarize information about center outcomes for a specific condition (eg, chronic lung disease), and (4) summarize annual outcome data to be used to influence policy and as a basis for public health programs designed to improve outcomes. Outcomes of interest may include rates of growth failure, cerebral palsy, mental retardation, or developmental delay; hearing impairments, vision impairments, or autism; need for technologic support such as home oxygen, ventilators, tracheostomies, or gastrostomies; and educational resources needed. Information about center outcomes for specific conditions and specific gestational ages also allows staff caring for high-risk infants to counsel parents with regard to prognosis.⁹ Providing comprehensive feedback of each evaluation to the family and the primary provider with appropriate counseling and referrals supports the concept of an effective medical home for NICU graduates.

Research

Follow-up results of populations enrolled in RCTs and well-designed cohort studies are needed to evaluate the long-term impact of interventions designed to improve the outcome of high-risk populations and identify previously unknown safety problems.

OBJECTIVE 2: DETERMINE WHO NEEDS TO BE FOLLOWED AND WHAT THE IMPORTANT RISK CATEGORIES ARE

Identified risk factors for adverse neurodevelopmental outcome in preterm and term infants identified in studies to date are listed in Table 1. Infants should receive follow-up assessments based on the severity of the perinatal problems, the interventions received in the NICU, the demographic risk factors of the infants' families, the outcome profile of the cohort in the individual NICU, and the NICU's resources. At a minimum, the follow-up cohort should include extremely low birth weight (ELBW) infants ≤ 1000 g birth weight and/or ≤ 28 weeks' gestation and term infants with hypoxic ischemic encephalopathy or severe hyperbilirubinemia requiring exchange transfusion. In addition, it is recommended that all children, especially those cared for in a NICU, have the benefit of periodic preventive assessments by their primary care physicians within the context of a medical home. The guidelines established for the periodicity schedule developed by the Committee on Practice and Ambulatory Medicine¹⁰ in consultation with national committees and sections of the American Academy of Pediatrics include regular basic assessments of growth, sensory function, behavior, and neurodevelopment. Infants with suspect findings and families with parenting challenges should be referred for additional, more comprehensive evaluation to their follow-up program, child development center, and additional community resources as needed. Moreover, follow-up care in a follow-up program or by the primary care provider should include counseling and support for families and communication among all participants in the medical home. Evaluation of the family should include information on adequacy of parenting skills, use of drugs, alcohol, and/or cigarettes, parent physical and mental health status, and adequacy of finances and health insurance. Referrals need to be facilitated by the medical home, as needed, with input from the family. Early-intervention parent groups, NICU parent groups, Family Voices, and community mental health services may be beneficial.

Risk Factors for Preterm (≤ 32 Weeks or Very Low Birth Weight, ≤ 1500 g) Infants

The developing brain of the premature infant is extremely vulnerable to injury. The long-term consequences of such injury include motor deficits commonly referred to as cerebral palsy (a nonprogressive injury of the central nervous system (CNS) characterized by abnormal control of movement and posture) as well as cognitive and behavioral problems.¹¹⁻¹⁹ The risk for neurodevelopmental deficits increases with decreasing gestational age, resulting in relatively high risk of cerebral palsy, developmental delay, hearing and vision impairment, and subnormal academic achievement among ELBW infants.^{4,8,11} These performance deficits are thought to be related to the increased biological vulnerability to injury of the basal ganglia, hippocampus, and periventricular white matter in premature in-

TABLE 1. Defined Risk Categories in the Term and Preterm Infant

Infants	Preterm	Term
Biologic risk	VLBW infants \leq 1500 g birth weight ELBW infants \leq 1000 g birth weight Infants with cranial ultrasound abnormalities including PVL-intraventricular hemorrhage, linear hyperechogenicity, Other neurologic problems (seizures, hydrocephalus) NEC Chronic lung disease Complex medical problems Small for gestation Higher-order multiples Twin-twin transfusion Complex congenital anomalies Recurrent apnea and bradycardia Hyperbilirubinemia requiring exchange Failure to grow in the NICU Sepsis, meningitis, nosocomial infections Multiparity Abnormal neurologic exam at discharge	Encephalopathy persisting at discharge Other neurologic problems/meningitis Complex medical problems Small for gestation Twin-twin transfusion Complex congenital anomalies Birth defects Metabolic disorders Sepsis, meningitis, nosocomial infections Hyperbilirubinemia requiring exchange Failure to grow in the NICU Multiparity Abnormal neurologic exam at discharge
Interventions	Resuscitation Postnatal steroids High-frequency ventilation Prolonged ventilation $>$ 7 days Total parenteral nutrition Prolonged oxygen requirements Nutritional therapies Other medications Surgical interventions for NEC, patent ductus arteriosus, shunt	Resuscitation Postnatal steroids High-frequency ventilation Prolonged ventilation $>$ 7 days Total parenteral nutrition Prolonged oxygen requirements Nutritional therapies Other medications Surgical intervention for NEC, shunt
Social/environmental	Low maternal education, teen mother Low SES: Hollingshead, ³² Hauser ³³ Single marital status Minority status No insurance or Medicaid insurance Low income Drugs/alcohol, smoking, substance abuse No prenatal care Environmental stress	Extracorporeal membrane oxygenation Low maternal education, teen mother Low SES: Hollingshead, ³² Hauser ³³ Single marital status Minority status No insurance or Medicaid insurance Low income Drugs/alcohol, smoking, substance abuse No prenatal care Environmental stress

fants.^{20–23} Risk for cerebral palsy and neurodevelopmental disabilities can be predicted in part from specific abnormalities on neonatal cranial ultrasound or magnetic resonance imaging (MRI); however, cognitive and behavioral problems may occur in the absence of identified neonatal neuroimaging abnormalities.¹³

Factors That May Affect Outcome: Biological Factors

Periventricular-intraventricular hemorrhage is the most common CNS lesion in the premature infant, which in its mildest form is confined to the germinal matrix and in more severe cases is complicated by bleeding into the adjacent ventricular system and/or white matter. Long-term neurodevelopmental deficits are strongly linked to these severe lesions.^{16,17} Approximately 26% of infants with birth weights between 501 and 750 g and 12% of infants with birth weights between 751 and 1000 g develop the more severe forms of CNS hemorrhage.¹⁸

Periventricular white matter injury (or periventricular leukomalacia [PVL]) may be identified on cranial ultrasound or MRI by the appearance of cystic lesions.¹² Cystic PVL is invariably associated with significant motor and cognitive deficits. Nonprogressive ventriculomegaly, secondary to loss of cortical

mass, is also associated with increased risk of neurodevelopmental deficit.²⁰ Linear hyperechogenicity within the thalamo-striatal ganglia of premature infants also has been associated with lower mental and developmental behavioral scores.²¹

Severe preterm delivery, male gender, sepsis, meningitis, necrotizing enterocolitis (NEC) requiring surgery, chronic lung disease/prolonged ventilation, severe growth restriction ($<$ 10th percentile for age and gestational age), and posthemorrhagic hydrocephalus have been identified as risk factors for adverse neurodevelopmental outcome in neonatal follow-up databases.^{18,19} Additional risk factors identified include multiple birth, medical complications in the NICU, and congenital abnormalities requiring medical or surgical intervention. Finally, research suggests that environmental stress in the NICU may be an important risk factor. For example, experimental evidence from animal models implicates environmental stress in the genesis of hippocampal injury.^{22–24}

Therapeutic Interventions

Perinatal interventions may affect neurodevelopmental outcome. For example, a large RCT and many large observational studies have documented that a

single course of antenatal glucocorticoid therapy matures the fetus and improves survival, skin integrity, and renal function and decreases periventricular/intraventricular hemorrhage.²⁵⁻²⁷ In contrast, prolonged postnatal steroid therapy to prevent or ameliorate chronic lung disease seems to be associated with negative CNS outcomes.^{19,28-30} Prolonged exposure to glucocorticoids in the animal model is associated with reductions in regional cerebral blood flow, specifically to hippocampus, with concomitant histologic changes, significant reduction in hippocampal volume, down-regulation of myelin basic protein and proteolipid protein in white matter, delayed myelination of optic axons, hyperactivity of the hypothalamic-pituitary-adrenal axis, and alterations in dopamine receptor responses.³¹

Family/Environmental Characteristics

The social and/or environmental characteristics of families³²⁻³⁵ become increasingly important as the child matures. Assessment of socioeconomic status (SES) in an individual or family unit is an indirect rather than direct measure of the social environment of the family. Mother-child interaction is a more proximal factor and is more predictive of earlier outcome ≤ 2 years, whereas SES is a status or distal factor and is more predictive of later outcome.³⁶ In a review of social class and developmental outcomes in 37 studies conducted in 2000,³³ low social class, as determined by several different means, was associated with poorer growth, greater academic difficulties including reading and spelling problems, lower IQ, poorer language skills, poorer fine motor skills, more aggression and externalizing behavior, more depression and other psychiatric disorders, poorer sibling relationships, and poorer social development. However, social class did not consistently predict symbolic play in infants or Bayley Mental Development Index (MDI)³⁷ and Psychomotor Developmental Index (PDI) scores up to 2 years. Although indicators of social class are effective predictors for a number of developmental outcomes, it must be recognized that effects are mediated by the child characteristics, family characteristics, and external supports.

The most common single measures used to assess SES are family income, educational level, and occupation. The easiest information to obtain is maternal educational level, but it may be only weakly related to the current status of the family. Although income may be more closely related to the family's current SES status, many respondents are uncomfortable about disclosing their income or uncertain about the actual amount. To overcome these problems, research protocols typically ask for income category, which is easier for the respondent but poses statistical challenges because categories are not continuous variables. The most common composite measure of SES is the Hollingshead³² Index of Social Prestige, which is a weighted average of educational and occupational levels. Years of education completed are classified into 7 categories, and occupations are classified into 9 categories of increasing status. The Hollingshead scale has the advantage of combining edu-

cation and occupation across 1 or 2 adult wage earners in the household as an algorithm for classification into SES levels. An important disadvantage is that the original combination rules are designed for nuclear families. Other disadvantages are that the Hollingshead Scale is insensitive to heterogeneity within a social class category, and the categories for occupation were developed almost 30 years ago. Inclusion of income level or percent of poverty level provides better discrimination among families.³⁴ Composite scores that combine several SES indicators and a standardized assessment of the home environment (Caldwell's HOME scale³⁸) have been used to overcome some of these limitations. The HOME scale is highly predictive of school performance but is generally too expensive for standard use.³⁹ Attempts to define a question or set of questions that capture family-life characteristics, eg, monthly rent or mortgage,³⁴ as recommended by the World Health Organization for the developing world, have been less successful in the United States, because many of the questions are subject to non-SES influences. Overall, the Hollingshead Scale is a solid measure and remains a powerful predictor of outcome. It is one of the best measures of poverty, single-parent families, and the lifetime consequences of low education.

Any analysis of differences between study groups that does not account for SES either by equivalent groups or statistical adjustment may be flawed, because SES may be an important moderator of perinatal risk and developmental outcome. The choice of how to manage the variance accounted for by SES depends on the study hypothesis. SES is frequently adjusted even with equivalent groups to reduce error variance. With very preterm infants or infants sustaining biological insult, there can be an interaction between perinatal risk status and SES such that high-risk infants raised in high-SES families have more positive outcomes, whereas those raised in low-SES families have poorer outcomes.³⁹ There are numerous additional environmental factors that have been shown to be associated with outcomes, including maternal depression, substance abuse, crowding in the home, and availability of educational materials and early-intervention services. Investigators must identify which variables are important at their center and which variables contribute to the specific research question being asked. In addition, most programs currently collect data on resource utilization, including early intervention, physical therapy, occupational therapy, speech therapy, day care, specialized educational services, and rehospitalizations. These data are collected to determine if the child is receiving adequate services so that referrals can be made or information shared as needed. In addition, resource utilization is an important variable to be evaluated in outcome studies.

OBJECTIVE 3A: DETERMINE THE OPTIMAL AGES OF ASSESSMENT

Although long-term follow-up of complete cohorts is optimal for determining the ultimate function of high-risk infants and the safety of antenatal and pre-

natal interventions, most follow-up studies are short-term (≤ 2 years). The selection of age of assessment is driven by several factors: developmental acquisitions available at a given age; availability and applicability of appropriate test instruments at specific ages; trends found in extant studies; and the cost and feasibility of long-term tracking in the population in question.

Assessment schedules should reflect the question asked in a specific research protocol. For surveillance purposes, a center may propose periodic enrollment (eg, ELBW infants may be enrolled for 1 year every 5 years and followed for 5 years, after which a new cohort may be enrolled).

In many NICU programs, all very low birth weight (VLBW) infants are referred to early intervention at the time of discharge from the NICU. Eligibility for early-intervention services, however, varies by state. If a developmental assessment is needed before 12 months to establish eligibility for a referral to an infant stimulation program, a 6- to 8-month corrected-age evaluation is recommended, using the *Bayley Scales of Infant Development-II* (BSID-II) MDI. The utility of assessment before this age is questionable.

12 Months' Corrected Age

Environmental factors are less influential on performance at 12 months' corrected age, and biomedical issues such as oxygen supplementation for chronic lung disease have resolved and may be less intrusive on testing procedures. By 12 months' corrected age, a more varied behavioral repertoire is available, and cognitive processes and emerging language can be assessed. Evaluation at this age also encourages family involvement in the program. However, cognitive and motor functions are still highly intertwined at 12 months' corrected age, and the period of developmental acquisition is a time of variability. Also, some neurologic abnormalities that are identified in the first year of life are transient or improve, whereas findings in other children may worsen over time.⁴⁰

18 to 24 Months' Corrected Age

By 18 to 24 months' corrected age, environmental factors begin to exert a stronger influence on test results, cognitive and motor abilities diverge, language and reasoning skills are developing, and there is improved prediction to early school-age performance.⁴¹⁻⁴³ A potential problem is that many intelligence tests have weak floors at this age, thereby restricting use to developmental tests, and therefore impairments may be overestimated or underestimated. Application of corrected age (the sum of chronologic age in weeks minus the difference between gestational age at birth and 40 weeks' gestation) to 2 or 2 1/2 years is controversial but generally accepted.^{44,45} Standard follow-up for many multicenter networks is currently at 18 to 24 months' corrected age.

3 to 4 Years

At 3 to 4 years, "intelligence" can first be assessed, as well as concept development, preacademic skills, early indicators of executive function, and visual-

motor integrative abilities. Verbal and nonverbal skills can be better differentiated. There is also an acceptable level of prediction⁴⁶ from scores at this age to later IQ scores. SES and social support, as well as other environmental factors, influence test results more strongly from age 3 years onward.

6 Years

By 6 years of age, a variety of tests and procedures can be used, and attention problems and school achievement (approximately first grade) can be assessed. The array of possible tests that can be used is more restricted at age 5 than at age 6.

8 Years

IQ, neuropsychological function, learning disabilities, school performance, and behavioral adjustment can be adequately assessed at 8 years (approximately third grade). IQ measured at 8 years predicts later IQ more accurately than at earlier ages.

OBJECTIVE 3B: DETERMINE THE APPROPRIATE ASSESSMENTS FOR ADMINISTRATION AT THE RECOMMENDED AGES

Ten different domains of development were identified and are related to age of assessment in Table 2. Three areas are basic (growth, neurologic status, and developmental status) and should be included in every follow-up program. The measures presented are based on the extensive experience of the participants in the workshop. It is anticipated that the information provided will assist follow-up programs to make choices based on this report and practical considerations.

Growth

Assessment of growth should include birth weight, birth length, and birth head circumference relative to an appropriate growth chart and an accurate determination of gestational age at birth. The most commonly used fetal growth charts are those of Lubchenco et al^{47,48}; however, these charts reflect preterm deliveries at ~ 1 mile above sea level. The intrauterine growth standards developed by Usher and McLean⁴⁹ do not reflect the cohort at greatest risk (22-24 weeks' gestation); they were published in 1969 for infants between 25 and 44 weeks' gestation. More recent population-based intrauterine growth standards have been published for the Canadian population for infants between 22 and 44 weeks' gestation.⁵⁰ The NICHD Neonatal Research Network uses fetal growth charts developed by Alexander et al⁵¹ that provide reference weights for infants born from 20 to 38 weeks' gestation for US infants. These fetal growth charts are often used to plot postnatal growth, although the environmental and metabolic demands of postnatal growth are very different from those during fetal development. The NICHD Neonatal Research Network has developed postnatal growth charts for VLBW infants⁵²; however, these growth trajectories should not be considered optimal, because $\sim 15\%$ of VLBW infants have a weight ≤ 10 th percentile at birth but 90% are ≤ 10 th percentile for their corrected fetal age at hospital discharge.

TABLE 2. Basic Categories of Assessment by Age

Area of Assessment*	3-4 and 6-8 mo CA	12-14 mo CA	18 mo CA	3-5 y	School Age
Growth* Nutrition	Wt, Lt, HC BMI, skinfolds Caloric/protein fat intake; energy expenditure Standard for age Amiel-Tison ⁵⁵	Wt, Lt, HC BMI, skinfolds Caloric/protein fat intake; energy expenditure Standard for age Amiel-Tison ⁵⁵	Wt, Lt, HC BMI, skinfolds Caloric/protein fat intake; energy expenditure Standard for age Amiel-Tison ⁵⁵	Wt, Lt, HC BMI, skinfolds Caloric/protein fat intake; energy expenditure Standard for age Amiel-Tison ⁵⁵	Wt, Lt, HC BMI, skinfolds Caloric/protein fat intake; energy expenditure Standard for age ⁴⁹⁻⁵⁴
Neurologic* assessment	Standard for age Amiel-Tison ⁵⁵	Standard for age Amiel-Tison ⁵⁵	Standard for age Amiel-Tison ⁵⁵	Standard for age Amiel-Tison ⁵⁵	Standard for age ⁴⁹⁻⁵⁴
Neuroimaging Research ^{*58-66}	Conventional MRI, DTI, DWI, CT	Conventional MRI, DTI, DWI, CT	Conventional MRI, DTI, DWI, CT	Conventional Functional, MRI, DTI, DWI, CT	Conventional Functional, MRI, DTI, DWI, CT
Gross motor* Development	Bayley PDI	Bayley PDI	Bayley PDI	GMFCS IQ, visual-motor skills, ADHD (age 5)	GMFCS IQ, Visual-motor skills, reasoning, memory, ADHD, executive function
School age research*	Bayley MDI Bayley PDI	Bayley MDI Bayley PDI	Bayley MDI Bayley PDI		School placement; achievement; executive function; academic performance; abdominal circumference
Language	Limited for young children; parent checklist	Limited for young children; parent checklist	Limited for young children; parent checklist	Limited for young children; parent checklist; PPVT ¹⁰¹ ; Grammar TEGI ¹⁰⁴	Limited for young children; PPVT ¹⁰¹ ; Grammar TEGI ¹⁰⁴
Functional Behavior		WeeFIM ⁹⁵ , Vineland ⁹⁶ ; PEDJ ⁹⁸ CBCL ^{109,110}	WeeFIM ⁹⁵ , Vineland ⁹⁶ ; PEDJ ⁹⁸ CBCL ^{109,110}	WeeFIM ⁹⁵ , Vineland ⁹⁶ ; PEDJ ⁹⁸ CBCL ^{109,110} , TOVA (4-5) ⁹⁰ ; GDS (4-5) ¹¹⁶	WeeFIM ⁹⁵ ; Vineland ⁹⁶ ; PEDJ ⁹⁸ CBCL ^{109,110} ; Conners CPT ⁷³ ; Conners RS ^{111,112}
QOL research*		QOL; HRQL; health status	QOL; HRQL; health status	QOL; HRQL; health status	QOL; HRQL; health status

CA, indicated corrected age; Wt, weight; Lt, length; HC, head circumference; BMI, body mass index; GDS, Gordon Diagnostic System; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; CT, computed tomography imaging; WeeFIM, Functional Independence Measure for Children; Vineland, Vineland Social Maturity Scale; PEDJ, Pediatric Evaluation of Disabilities Inventory; PPVT, Peabody Picture Vocabulary Test; TEGI, Test of Early Grammatical Impairment¹⁰⁴; Conners RS, Conners Teacher Rating Scale¹¹¹ and Parent Rating Scale.¹¹²

* Research protocols (auditory CPT) can be measured at later ages,⁸¹ and verbal IQs can be obtained.

Weight, length, and head circumferences should be collected routinely and serially in all programs by examiners trained to reliability using standard techniques. For children ≤ 2 years, weight should be obtained with the child completely undressed. Recumbent length is obtained until age 2 by using a pediatric length board, and maximal occipital frontal head circumference is recorded to the nearest millimeter by using a nonstretch measuring tape. Anthropometric measures in the United States are plotted according to gender and age (adjusted until age 2) on National Center for Health Statistics growth charts. Poor growth is defined as weight, length, head circumference, or weight-to-length ratio ≤ 10 th percentile.⁵³ Other measures of growth used in research protocols include skinfold thickness,⁵⁴ calculated measures of weight-to-length ratios, growth velocity, protein and caloric intake, energy expenditure, and bone density.

Neurologic Outcome

The neurologic examination of the toddler and older child^{40,55-57} is an integral part of the neurodevelopmental follow-up assessment, yet it remains poorly described and standardized in many research protocols. This early assessment can identify infants with mild, moderate, and severe abnormalities. This assessment is of interest because infants with mild or transient neurologic abnormalities often improve over time, unlike infants with severe early neurologic dysfunction, who are less likely to improve and have the worst neurodevelopmental outcome.⁴⁰ The neurologic examination of the toddler and older child can be used to determine resource needs such as early intervention. Follow-up programs need to develop a manual of operations for the entire assessment, use a standardized neurologic examination, establish definitions, and train and certify examiners to reliability on an annual basis. Components of the examination should include assessment of gross motor function, tone, reflexes, cerebellar function, cranial nerves, and language. In addition, excellent observation skills, adherence to examination protocol, good interpersonal skills, and flexibility are the key to an accurate assessment of the young child; much can be learned by observation of posture, movement, and quality of movement before the onset of the "formal" examination.

Imaging

The application of MRI to predicting outcome in high-risk children or for evaluating them later in life is an evolving field.⁵⁸⁻⁶⁶ Conventional MRI is effective for detecting developmental abnormalities of the CNS and PVL virtually any time after birth. Diffusion magnetic resonance methods measure changes in water apparent diffusion coefficient and are used as an early indicator of brain injury becoming sensitive 2 to 5 days after injury in infants. T1- and T2-weighted images also detect CNS injury, although their sensitivity varies with the time after the injury. Conventional T1- and T2-weighted MRI is routinely used to assess myelin development and maturation status in children and preterm infants. Functional

MRI may be used to assess the cortical reorganization associated with injury and recovery. These techniques and the development of age-based norms are under continuous development. Imaging technologies are currently being used in the NICU to evaluate CNS injury to determine risk category and potential postdischarge needs and to predict outcome. Current studies are evaluating the use of MRI in older children to evaluate the association between neurocognitive skills and brain injury.

Gross Motor Skills

Specific tests of gross motor function are currently frequently combined with the standard neurologic examination. The Gross Motor Function Classification System (GMFCS)⁶⁷ is the first reliable and validated system available to describe the severity of motor dysfunction in children with cerebral palsy and has been shown to be reasonably stable between the ages of 2 and 12 years.⁶⁸ The GMFCS for cerebral palsy provides classification of age-adjusted variations in 5 levels of gross motor function, with the highest level of mobility expected between 6 and 12 years of age. Descriptions are available for children < 2 years, 2 to 4 years, 4 to 6 years, and 6 to 12 years. The GMFCS is quick and easy to use; classification is made by determining which level best represents the child's present abilities and limitations in gross motor function. The description for each level is broad and not intended to describe all aspects of the motor function of individual children. Distinctions between levels of gross motor function are based on functional limitations, the need for assistive mobility devices (eg, walkers, crutches, canes), wheeled mobility, and, to a lesser extent, quality of movement. The scale is ordinal, with no intent that the distances between levels be considered equal or that children with cerebral palsy are equally distributed among the 5 levels. The 5 levels of function (level 1 is the highest) are:

1. Walks without restrictions; limitations in more advanced gross motor skills
2. Walks without assistive devices; limitations walking outdoors and in the community
3. Walks with assistive mobility devices; limitations walking outdoors and in the community
4. Self-mobility with limitations; children are transported or use power mobility outdoors and in the community
5. Self-mobility is severely limited even with the use of assistive technology

The algorithm shown, based on the GMFCS, was developed to classify infants at 24 to 28 months' corrected age in the NICHD- and National Institute of Neurologic Diseases and Stroke-sponsored randomized clinical trial of the Beneficial Effects of Antenatal Magnesium Sulfate in the Maternal Fetal Medicine Units Network (Fig 1). In addition, the characteristics of upper extremity function including bimanual function and bilateral pincer grasp are needed to differentiate among right hemiplegia, left hemiplegia, diplegia, and other minor motor impairments.

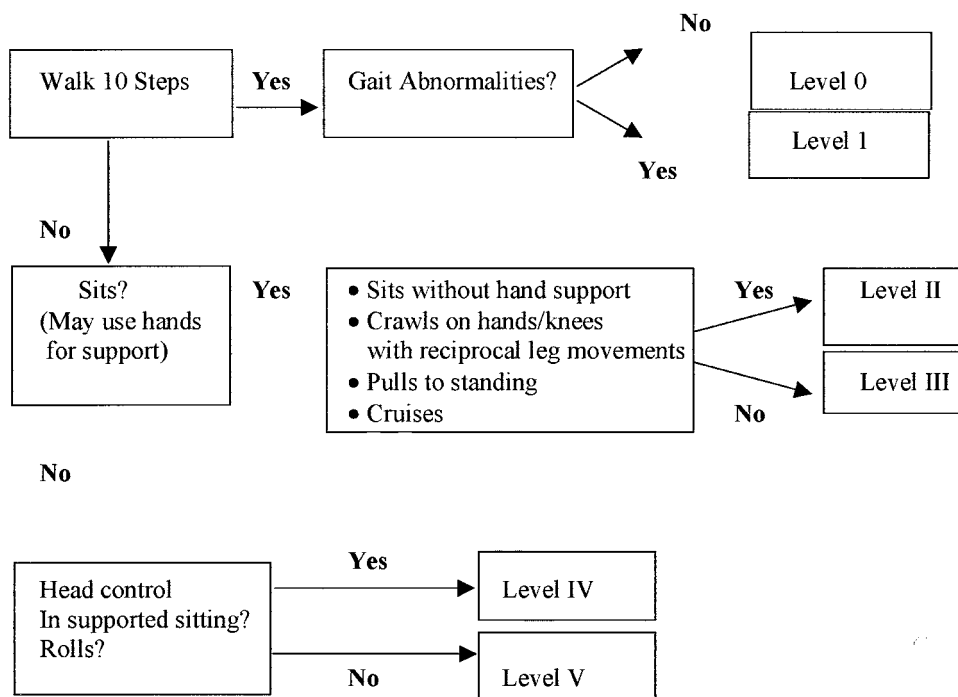


Fig 1. Gross motor function classification system at 24 months corrected age.

Cognitive and Developmental Skills

The emergence of high-prevalence/low-severity dysfunction (borderline IQ, learning disabilities, attention-deficit/hyperactivity disorder [ADHD], neuropsychologic deficits, and behavior problems) in children at biological risk has underscored the need for detailed assessment of cognitive development. Although major deficits can be detected in infancy, more subtle high-prevalence/low-severity dysfunctions become increasingly obvious as the child grows older, which is assumed to be because of continued cortical development and increased demands for performance in emerging areas of cognitive function. Moreover, there is some evidence that the cognitive function of infants with severe CNS injury tends to deteriorate over time, whereas the cognitive scores of neurologically intact but immature infants tend to improve as they mature.⁶⁹ These data support the importance of long-term follow-up to obtain school-age outcomes on high-risk infants.

IQs

Earlier meta-analyses of cognitive deficits in low birth weight (<2500 g) infants indicated a 5- to 7-point deficit in comparison to term infants. More recent comparisons suggest a 0.3- to 0.6-SD decrease in IQ in children born prematurely, producing a reported decrement that ranges from 4.5 to 9.0 points. Therefore, in VLBW infants free of major disabilities, mean group IQs fall in the borderline to average range, with low average scores being the mode. However, use of IQ scores masks more subtle deficits; a verbal, performance, or area index score is the average of various subtests (ie, verbal comprehension, processing speed, etc), whereas a full-scale IQ is an average of averages. IQ scores are influenced

by socioeconomic variables, particularly with respect to verbal function.

Visual-Motor Skills

The majority of children born at ELBW and VLBW, even those with average IQs, manifest visual-motor problems that include deficits on neuropsychological tasks such as copying, perceptual matching, spatial processing, finger-tapping, pegboard performance, visual memory, and visual-sequential memory. Estimates of visual-perceptual and visual-motor integration problems are in the 11% to 20% range; fine motor problems are as high as 71%. These deficits seem mostly related to biological risks rather than environmental risks.

Neuropsychological Functions

Preliminary data suggest an increased incidence of executive-function problems in planning, organization, problem-solving, working memory, and inhibition as well as attention. Related to this, a sizeable number of children born VLBW display nonverbal learning disabilities (in which verbal cognitive skills are better developed than nonverbal abilities, producing verbal IQ/performance IQ discrepancies) and associated problems in visual-motor integration, visual perception, mathematics, spatial skills, and fine motor speed. Verbal abstracting, reading comprehension, written output, and social skills are also areas of deficit with nonverbal learning disabilities. Neuropsychologic deficits are related to both biological and environmental risks.

The array of potential problems found in the follow-up of preterm infants mandates that assessment extend beyond traditional IQ and achievement testing. The pattern of developmental change or im-

provement may be more informative than the mid-point score in a given area of function. These process issues, which have often been overlooked, may be informative and useful for intervention and predictive purposes. Assessment of intelligence in follow-up studies to school age should include 5 key elements: reasoning, knowledge, quantitative reasoning, visual/spatial processing, and working memory.

Areas of Assessment

Specific tests and rating scales that assess the following areas should be considered in follow-up protocols (those falling under a broad categorization of “cognitive” are in italic type):

1. *Intelligence* (including verbal and nonverbal aspects) and *executive function*
2. Achievement
3. Functional status (self-care, mobility, communication)
4. Language (phonological awareness, syntax, verbal fluency, comprehension of instructions, speed naming, higher-order abstracting functions)
5. *Sensorimotor functions* (visual-motor precision, fine motor speed)
6. *Visual spatial processes* (design-copying, visual closure)
7. *Memory and learning* (list-learning, delayed recall, narrative memory, and use of semantic/strategic and rote/episodic verbal and visual tasks)
8. Behavioral adjustment (*ADHD*, internalizing and externalizing behaviors, and social functioning).

Table 3 lists specific tests recommended to evaluate developmental/cognitive function.^{70–85} Tests in the first row are those considered most desirable, and tests in subsequent rows are acceptable alternatives; listed tests are not necessarily all administered at any given time. Moreover, some tests have not been included because of lack of valid test norms or because they do not sample cognitive constructs of interest. Finally, certain functions (eg, visual perception) may be measured on several different tests (eg, Neuropsychological Test [NEPSY]⁷⁸ and Motor Free Visual Perception Test⁸⁶).

Most IQ tests require so-called level C qualification

for administration, meaning that they should be administered by qualified masters-level or above psychologists: pediatric, clinical, child, and school psychologists and child neuropsychologists. Centers that use limited assessment batteries because of limitations of staff or funding require level B qualifications for administration. Examples of these tests include the Bayley Infant Neurodevelopmental Screener (BINS),⁸⁷ Kaufman Brief Intelligence Test,⁸⁸ Developmental Test of Vision Motor Integration,⁷⁰ rating scales, and similar instruments. Adequately trained support staff can administer level B tests, and appropriately trained developmental pediatricians and psychologists can administer the BSID-II.³⁷

Minimizing Barriers to Assessment

Assessment of children with sensorimotor impairments remains challenging for new examiners. Children with visual impairment are extremely difficult to evaluate before the preschool age, because most test items are sensorimotor in nature. Evaluation is restricted to verbal behaviors and gross motor milestones. The Mullen Scales of Early Learning,⁸⁹ Language Receptive Organization (LRO), and Language Expressive Organization (LEO) scales may be useful for children with vision impairment, although items of an “intersensory” (ie, auditory and visual) nature are eliminated or scored in a prorated fashion. With increasing age, verbal subtests can be used, although many still require viewing pictures and then producing a response. Auditory memory as well as auditory attentiveness can be measured with the auditory Continuous Performance Test (CPT)⁷³ at later ages, and verbal IQs can be obtained. The standard use of the BSID-II is not appropriate for children who are legally blind.

Hearing impairment precludes adequate assessment of verbal abilities; sensorimotor subtests can be administered, but an overall BSID-II MDI cannot be computed. The Mullen Scales of Early Learning⁸⁹ may be considered, using the LRO and LEO scales for children with hearing impairment, although intersensory items (requiring hearing and vision or hearing and motor skills) must be addressed. With increasing age, nonverbal tests can be used (allowing computation of nonverbal indexes), but the hearing-

TABLE 3. Comprehensive Cognitive Assessment Protocol

12 mo CA	24 mo CA	3–4 y	6 y	8 y
BSID-II ³⁷	BSID-II ³⁷	DAS ⁷⁵	WISC-IV ⁸⁵	WISC-IV ⁸⁵
MDI and PDI	MDI and PDI	BSID-II (36 mo)		
Bayley MDI	Bayley MDI	McCarthy ⁷⁹	WASI ⁸⁴	WASI ⁸⁴
		Stanford Binet-V ⁸¹	Stanford Binet-V ⁸¹	Stanford Binet-V ⁸¹
		WPPSI-III ⁸³	NEPSY ⁷⁸	NEPSY ⁷⁸
		Bracken Basic Concepts-R ⁷¹	VMI ⁷⁰	BRIEF ⁷⁶
			Grooved Pegboard ⁸⁰	Parent and teacher versions
		K-ABC ⁷⁷ (sequencing simultaneous processing subscales)	Conners CPT checklists ⁷³	Conners CPT checklists ⁷³
				WRAML ⁸² /CMS ⁷²
				CVLT-C ⁷⁴

DAS indicates Differential Ability Scale; MSCA, McCarthy Scales of Children’s Abilities; SB-V, Stanford-Binet V; WPPSI-IV, Wechsler Preschool and Primary Scale of Intelligence-IV; K-ABC, Kaufman Assessment Battery for Children; WISC-IV, Wechsler Intelligence Scale for Children-IV; WASI, Wechsler Abbreviated Scale of Intelligence; VMI, Developmental Test of Visual Motor Integration; BRIEF, Behavior Rating Index of Executive Function (questionnaire); WRAML, Wide Range Assessment of Memory and Learning; CMS, Children’s Memory Scale; CVLT-C-California Verbal Learning Test–Children’s Version.

impaired child still may find it difficult to understand directions and provide the required response. In these settings, performance IQs can be derived, and visual CPTs,⁷³ visual memory tasks,⁹⁰ visual-motor integration,⁷⁰ rating scales, and more specific neuropsychological tests may be used. The Leiter International Performance Scales-R⁹¹ is a useful test for use in the hearing-disabled population (2–20 years), because auditory skills are not required.

Finally, it is important to realize that the reference norms of most tests are children without sensory impairments; hence, administration to children with visual or hearing deficits may affect the tests' psychometric qualities. The NICHD protocol codes specifically for children who have a sensory loss (code 6 indicates that the child cannot be tested but appears normal; code 5, the child cannot be tested but appears to be mild to moderately delayed; code 4, the child is severely developmentally delayed). For the child classified as severely developmentally delayed, a Bayley score of 49 is assigned.

Assessment of cognitive abilities in children with motor impairments is particularly difficult before preschool because of the interweaving of cognitive and motor function. Substantial alterations of test procedures are necessary that, in turn, may have an impact on comparability to norm-referenced data. Subsequently, verbal tasks as well as nonverbal tasks that do not require a motor response (eg, matrices) can be used. Assistive devices/technology also may be used in such situations. Tests recommended for programs with comprehensive follow-up protocols include the Differential Ability Scales,⁷⁵ McCarthy Scales of Children's Abilities,⁷⁹ Stanford Binet,⁸¹ Wechsler Intelligence Scales for Children,⁸⁵ Kaufman Assessment Battery for Children,⁷⁷ Wechsler Preschool and Primary Scale of Intelligence-III,⁸³ Wechsler Abbreviated Scale of Intelligence,⁸⁴ the NEPSY,⁷⁸ Developmental Test of Visual Motor Integration,⁷⁰ CPTs,⁷³ Behavior Rating Inventory of Executive Function,⁷⁶ Wide Range Assessment of Memory and Learning,⁸² Children's Memory Scale,⁷² and the California Verbal Learning Test-Children⁷⁴ (Table 3).

Cognitive tests recommended for programs with limited assessment protocols include the BINS,⁸⁷ the BSID-II MDI,³⁷ Ages and Stages,⁹² and the Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale⁹³ (CAT/CLAMS) (Table 4).

Additional assessments are brief versions of some of the tests listed in Table 3.^{70,73,77–79,84,85,88,94}

Functional Skills

Instruments for measuring functional status in essential activities of self-care, mobility, communication, and learning are assessed with the Functional Independence Measure for Children,⁹⁵ the Vineland Adaptive Behavior Scale,⁹⁶ the Battelle,⁹⁷ and the Pediatric Evaluation of Disability Inventory⁹⁸ psychometric properties of these assessments are shown in Table 5. Examination of the functional strengths and challenges of children with neurodevelopmental impairments provides additional information regarding disablement (attitudes, barriers, and policies that restrict opportunities) and enablement (supports that break down barriers). A similar assessment of functional skills obtained by parent interview was developed by Stein et al.⁹⁹ Functional assessments have important strengths including the need for a minimal database, use of criterion referencing, obtaining information on typical performance, and ability to measure severe disability. In addition, functional assessments can be administered to a reliable observer/informant by staff trained in a variety of disciplines and by telephone interview and may be linked to population surveys.

Language

Effective receptive and expressive language is fundamental for communication, adaptive behavioral and academic success, and literacy. Assessing receptive and expressive language is particularly challenging, because different language skills emerge and are mastered at different ages, the rate of development of different language skills is not linear, and different means of assessment are suitable for different ages. Comprehensive language testing including expressive and receptive language, organization, and grammar is required to obtain a complete assessment of language function. Parental checklists of expressive language are available including the McArthur¹⁰⁰ for ages ≥ 1 year. Receptive language can be tested from ages 2 to adulthood with the Peabody Picture Vocabulary Test-III.¹⁰¹ The combination of receptive and expressive language can be assessed with the Expressive One-Word Picture Vocabulary Test¹⁰² and the Receptive One-Word Picture Vocabulary Test.¹⁰³ Language organization can be assessed with the

TABLE 4. Limited Cognitive-Assessment Protocol

12 mo	24 mo	3–4 y	6 y	8 y
BINS ⁸⁷	BINS ⁸⁷	K-BIT ⁸⁸	WASI ⁸⁴	WASI ⁸⁴
Ages and Stage ⁹²	Ages and Stage ⁹²			
CAT/CLAMS ⁹³	CAT/CLAMS ⁹³			
BSID-II MDI ³⁷	BSID-II MDI ³⁷	WRIT ⁹⁴	4 subtests from WISC-IV ⁸⁵	4 subtests from WISC-IV ⁸⁵
		BSID-II MDI (3) ³⁷		
		McCarthy Screener ⁷⁹ /K-ABC ⁷⁷	Conners CPT ⁷³	Selected NEPSY ⁷⁸ subtests
		short form		Conners CPT ⁷³
		DTVMI ⁷⁰	DTVMI ⁷⁰	DTVMI ⁷⁰

K-BIT indicates Kaufman Brief Intelligence Test; WRIT, Wide Range Intelligence Test; WASI, Wechsler Abbreviated Scale of Intelligence; MSCA, McCarthy Scales of Children's Abilities; WISC-IV, Wechsler Intelligence Scale for Children Subtests; DVTMI, Developmental Test of Vision Motor Integration.

TABLE 5. Levels of Follow-up Program Intensity

Level 1	Level 2	Level 3	Level 4
Telephone interview to screen: developmental screeners; Ages and Stages ⁹² and CAT/CLAMS ⁹³	In-clinic single visit: growth; neurologic exam; screen; developmental screeners; Ages and Stages ⁹² and CAT/CLAMS ⁹³ developmental screeners: BINS ⁸⁷	Single visit: comprehensive assessment; growth; neurologic exam; developmental assessment (Tables 2 and 3) (behavior, other reduced comprehension or comprehension)	Serial comprehensive assessments: growth; neurologic exam; developmental assessment, behavior (may include videotapes, MRIs, actigraphy, parent IQ, telemedicine, biochemical parameters, genetics)
Refer for diagnostic or intervention services as needed	Refer for diagnostic or intervention services as needed	Refer for diagnostic or intervention services as needed	Refer for diagnostic or intervention services as needed
Collect data	Collect data	Collect data	Collect data
Clinical	Clinical	Clinical/Research	Clinical/Research

Mullen Scales of Early Learning,⁸⁹ which has both LRO and LEO scales. Assessment of grammar using the Rice/Wexler Test for Grammatical Impairment¹⁰⁴ targets elements of morphosyntax known to be weak in children with language impairments. It has strong predictive validity for children 4 to 6 years of age and has been standardized for ages 3 to 8 years. The Clinical Evaluation of Language Fundamentals III¹⁰⁵ is another language test that assesses higher-level language function for children ≥6 years.

Behavior and Attention

The choice of which behavioral domain to measure is a difficult decision for individuals designing a follow-up study. Target outcomes should be selected on the basis of theoretical and clinical concerns for the specific at-risk group. These concerns are combined with known stages of development to determine when to assess. Fig 2 describes the timeline for behavioral domains relevant to high-risk children. Cognition and motor control may be a higher priority among ELBW children, whereas psychopathology and antisocial behavior may be of greater concern in drug-exposed children. Specific methodology issues such as what measures to use, where to conduct the assessment, and how to train testers are guided by good research practices and practical consideration of time and resources.

In general, the easiest, least demanding method is parent report. The next easiest are tests and child interviews. The most difficult are procedures that require specific settings and extensive scoring. Com-

puter implementations have helped to bring some difficult procedures within reach (eg, Cambridge Neuropsychological Test Automated Battery,¹⁰⁶ Diagnostic Interview Schedule for Children,¹⁰⁷ and Test of Variables of Attention [TOVA]⁹⁰), but these tests are demanding in terms of equipment and software.

Parent questionnaires are useful in cases in which the child exhibits a behavior but is too young to self-report or when brief observation is insufficient to capture the outcome of interest. A behavior assessment administered by questionnaire is the Brief Infant-Toddler Social Emotional Assessment Version 1.0.¹⁰⁸ It is designed as a first step in the early identification of 1- to 3-year-olds with social-emotional problems and/or delays in social competence. It consists of 60 interview questions. A trained medical or nonmedical professional may administer this scale to the primary caretaker of the child. Estimated time to administer the Brief Infant-Toddler Social Emotional Assessment is 15 minutes. Another good example of a behavior assessment for children is the Achenbach Child Behavior Check List (CBCL).^{109,110} The CBCL is a comprehensive measure of parental perception of children’s behaviors designed to assess the social competencies and behavioral problems of children aged 2 to 3 (CBCL 2-3) and 4 to 18 (CBCL 4-18) in a standardized format. The CBCL provides norms for interpretation, can be administered by interview for parents with low reading skills, and has a simple yes/no response format. There are versions for teachers and adolescents, which can be useful. Re-

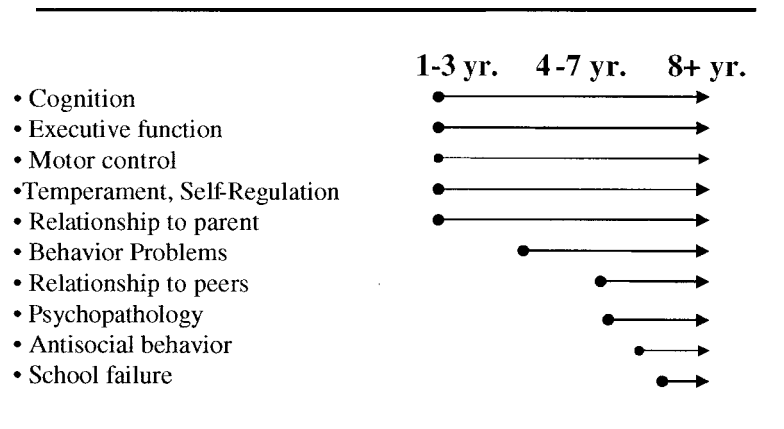


Fig 2. Timeline: child outcomes.

sults from all parent-report questionnaires must be interpreted with caution, because they reflect the parent's own bias and relationship with the child as well as the child's behavior. Therefore, it is probably best among school-aged children to have both parent and teacher versions. The Conners^{111,112} parent and teacher rating forms are frequently used when assessing school-aged children for attention deficit and hyperkinesis.

Parent and child report as well as tests are subject to sources of error. As noted, parent reports are subject to parental bias. Child reports are also subject to the child's desire to please or hide bad things and to the child's understanding of the questions and the response scale. Tests with good psychometric properties typically have highly constrained acceptable answers and strict instructions for administration. Thus, children's spontaneous responses and strategies, including how they reach their conclusion, are not typically measured.

For older children (7–17 years), the Children's Depression Inventory¹¹³ and the Behavior Assessment Systems for Children¹¹⁴ may be useful. The Behavior Assessment Systems for Children is a broad-band tool that provides a good representation of the child's behavioral functioning. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*¹¹⁵ criteria are used to establish diagnostic categories.

TOVA⁹⁰ is a computerized test that provides a continuous performance task involving sustained attention and response inhibition. It is less fun for the children by design but provides data that can be compared with norms (separately for girls and boys). The Gordon Diagnostic System,¹¹⁶ which is similar, is a microprocessor-based system with tasks for diagnosing attention deficits, especially ADHD. Both tests give insight into attention and impulsivity disorders. The Conners^{111,112} parent and teacher rating forms, which are frequently used when assessing school-aged children for attention deficit and hyperkinesis, differ somewhat but also give comparable information. Finally, the Diagnostic Interview Schedule for Children¹⁰⁷ has the advantage of generating psychiatric diagnoses without professional-level staff, which makes it accessible for a research study, but it is demanding for children, particularly those who are lower functioning.

School-Age Outcomes

Studies of school-age outcomes of high-risk children to date have been predominantly descriptive rather than hypothesis driven. Assessments have included measurement of growth; parent and teacher questionnaires concerning health, school performance, behavior and psychiatric disorders, quality of life (QOL), self-esteem, impact on the family, and examination and testing of children for neurosensory disorders, cognition, specific neuropsychologic and motor functioning, and academic achievement. The impact on society of the increased survival of high-risk children and the costs to the health and educational system at school age have not been fully examined.

At school age and older, it becomes important to

know how the children and their families function in the various outcome categories; however, a noncategorical combined or functional approach may provide better information concerning the overall impact of modern intensive care methods.¹¹⁷

The traditional assessment of high-risk outcomes based on specific diagnoses or problems has limitations. Health problems in normal child populations are reported to occur in clusters, with many children having >1 type of problem.¹¹⁸ Additionally, high health utilization tends to be associated with the presence of a variety of health problems rather than with a particular type of illness.¹¹⁹ Extremely preterm or high-risk children epitomize the pattern of multiple health and educational problems. Categorization of the medical, neurologic, developmental, and behavioral problems individually thus will not reflect the impact of the combined effects on their overall health status and health care and educational service utilization. The use of diagnostic labels has additional disadvantages in that there may be inconsistency in diagnoses. A diagnosis, furthermore, does not convey the extent of morbidity, especially functional consequences, for individual children, caregivers, and health and educational providers.

The noncategorical approach provides for comprehensive assessment of the functional impact of neonatal intensive care survival on health and psychological outcomes. It can be applied to meet various service- and policy-related objectives such as identification of needs for service, functional impact, and program eligibility for Title V programs.^{120,121} This approach does not preclude assessment of the obvious biological differences that distinguish one disease from another but complements the more traditional categorical approach. It has been advocated for perinatal outcomes research but has rarely been used.^{122–124}

The 2 health instruments based on the generic or noncategorical approach for late childhood and young-adult studies^{124–126} are the Child Health Illness Profile (CHIP-CE)¹²⁷ and the Questionnaire for Identifying Children With Chronic Conditions (QuICC).¹²⁸ The 2 questionnaires complement each other in that the CHIP-CE examines the profile of the child's general health and developmental status, whereas the QuICC examines functioning and special health care and educational needs attributed to chronic illness. The CHIP-CE includes 6 domains: (1) satisfaction with health, (2) discomfort, (3) achievement, (4) risk, (5) resilience, and (6) medical and psychosocial disorders. It is applicable from 6 to 11 years of age. The adolescent version (the CHIP-E¹²⁹) can be used from 11 years old until late adolescence. The QuICC incorporates the consequences of chronic physical, cognitive, psychological, and behavioral health conditions into 3 domains: (1) functional limitations, (2) dependence on compensatory mechanisms, and (3) need for services beyond routine care.^{128,130} It was developed for children with special health care needs. The Child Health Questionnaire (CHQ)¹³¹ is an instrument that has been designed and normed for children 5 to 18 years of age. The CHQ can be used independently or in conjunction

with Health Act condition-specific surveys in research or clinical settings.

QOL

There has been increasing interest in the parent and child perception of “well-being” regarding aspects of health that are relevant to the child and family, which has resulted in the concept of measurement of QOL.¹³² Although health status, functional abilities, and QOL are 3 different concepts, they are used interchangeably. Broadly speaking, QOL is an all-inclusive concept that incorporates many factors that impact on the life of an individual, of which health is only 1 domain. Health-related QOL (HRQL),^{132–135} on the other hand, is a multidimensional measure that takes into account all aspects of health and implicitly reflects the personal values of an individual. These values may be unrelated to disease state or severity. It is the characteristic of personal values that distinguishes HRQL from other measures of health. It is important to take into account the fact that young children are constantly developing and have varying capabilities that change over time.¹³⁶ In addition, their personal values also evolve over time and generally differ from adults in their views about QOL. Investigators recently attempted to involve older children in measuring their own HRQL. Others have also obtained parallel proxy ratings from parents.¹³⁷

Which Groups Should Have Measurement of HRQL

It is useful to learn from the personal perspectives of the premature children and their parents.^{135,137} To date, self-reported HRQL has been measured for infants of <1000-g birth weight at adolescence¹³⁷; recent studies of preschool-aged children have shown that, by parent report, the HRQL of infants <32 weeks' gestational age was significantly lower than that for infants ≥32 weeks' gestation and the reference group.¹³⁸ HRQL measures also may have the potential of providing complementary information on subjects in pediatric clinical trials, although little work has been done on this.

Practical Considerations

It is important that the HRQL measures include those aspects of functioning that are important to the child and family: they should reflect the multiple domains of age-appropriate activities, and they should be reliable, valid, and sensitive to changes in QOL of the child.^{136,139,140} In addition, because of the short attention span of the children, the questionnaires should be brief and impose as little burden as possible to the respondents and staff. It is also essential that the self-completed measures are phrased in ways that children can understand and are at the appropriate reading level of the child.

Strictly speaking, because HRQL measures are designed to reflect the personal perspective of the patient, it is not possible to accurately obtain the data from children younger than 7 to 8 years. However, investigators recently showed that young children are capable of recognizing their emotions, although they may have limited memory and ability to carry

out logical thinking of tasks. Given the opportunity and correct context, children as young as 7 years are able to answer questions regarding their own health status. However, at least grade 2 skills are necessary for rating the feeling thermometer, and grade 6 reading skills are required to complete the Standard Gamble technique.¹⁴¹ In older children, the opinion of the child should be sought whenever possible. Thus, unless parental proxy responses are obtained, it is not possible to obtain HRQL measures accurately for children <8 years old.

There are several modalities of administration of the HRQL measures: self-administered questionnaires at the study site, mailed questionnaires (self-administered at home), telephone interview, face-to-face interview questionnaires at the study site or home visit, and face-to-face interviews for younger children (<8 years) using interactive pictures, videos, and computer programs. A self-completed questionnaire at the study site is obviously the most cost-effective and suitable for older children and adolescents. A self-completed mailed questionnaire is also cost-effective but less reliable, and the response rates are lower than with other modes of administration.¹⁴² Telephone interviews achieve a higher compliance than mailed questionnaires, but the validity is questionable in young children. Face-to-face interviews are the most costly, but compliance is greater and the data are more reliable.¹⁴³

Finally, despite the growing literature, there continues to be skepticism by the medical community in accepting self-reported HRQL as relevant and valid information.¹³⁶ Eiser and Morse¹³⁶ suggests that QOL measures need to be used more routinely in evaluation of alternative treatments to understand the burden experienced by the family.

The following is a brief description of the available measures for young children:

1. The PedsQL¹⁴⁴ is a generic 23-item developmentally appropriate questionnaire for children aged 2 to 4, 5 to 7, 8 to 12, and 13 to 18 years. Pediatric self-report measures are available for children and adolescents aged 5 to 18 years, and parent proxy-report measures of child HRQL are available for children aged 2 to 18 years. A complementary PedsQL disease-specific measure for chronic health conditions is also available. The PedsQL is the only generic self- and proxy-reported pediatric HRQL instrument that spans a wide range of 2 to 18 years while maintaining items and scale.¹⁴⁴
2. The TACQOL¹⁴⁵ is a 108-item parent form that taps 7 domains and also measures the child's emotional reaction to his or her health problems.
3. The Quality of Life Preschool Children (TAPQOL) questionnaire¹³³ has 43 items, taps 12 domains, and is also weighted by the emotional response to problems in health states. In a study of preschool preterm infants between ages 1 and 4 years, who were infants of <32 weeks' gestation, differences were found between neonatologists' and parents' perception of the HRQL of preterm children.¹³⁸
4. The CHQ¹³¹ is a generic QOL instrument that has 14 unique physical and psychosocial concepts. A

parent-completed form is available for children 5 to 11 years of age (full-length, 50 items; short form, 28 items). In addition, a parent-completed Infant/Toddler Health Questionnaire with 8 infant concepts and 5 parent concepts is also available. The CHQ and Infant/Toddler Health Questionnaire essentially provide health profiles and do not have a evaluative component.

5. Health Status Classification System-PS^{146,147} is adapted from the widely used HU12/3 systems.¹⁴⁸ It is comprised of 12 dimensions encompassing a broad range of physical and developmental parameters, each with 3 to 5 levels per dimension.

OBJECTIVE 4: DETERMINE THE RELEVANT ISSUES RELATED TO SELECTION OF CONTROLS AND TRACKING OF SUBJECTS

Well-selected control populations with background variables similar to study subjects are important for the assessment of outcomes of high-risk children. Variables to consider in selecting controls include those related to sociodemographic status, ethnicity, gender, and age of the child. Measures of sociodemographic status most commonly used include parental education, age, marital status, type of health insurance, and area of residence. Maternal rather than paternal sociodemographic status is usually considered in the United States, because many mothers of high-risk children are unmarried, and the fathers may have little contact with their children. Siblings have been suggested as ideal controls, because they share the same sociodemographic and genetic background as the study child. However, siblings are rarely used, because they need to be of the same gender and of an age fairly close to that of the study child. Additional problems in using siblings are that they, themselves, are often preterm, and even if born at term gestation, their behavior and school performance may be influenced by having a “special-born” sibling.

Normal birth weight control populations are usually not needed when RCTs of perinatal therapies are undertaken. Normal birth weight controls are often not included when comparing the outcome of low-risk versus high-risk birth weight groups, eg, in studies assessing the effects of chronic lung disease, brain hemorrhage, jaundice, etc.¹⁴⁹

In contrast to school-age studies, descriptive studies of early-childhood outcomes of high-risk children (<3 years) have often not included control subjects. However, it is currently recommended that if the true impact of prematurity is to be identified, “normal” control populations should be included at all ages. In 1992, Gross et al¹⁵⁰ stressed the importance of concurrent controls, because the cognitive tests used in earlier time periods may be outdated. Experience with the BSID-II presents problems in that rates of cognitive impairment are overestimated when compared with those found at school age. In addition, average IQ scores increase by 0.5 points per year or 5 points per decade. Ideally, controls should be selected at birth by matching the study infant with the next born infant of the same race, gender, se-

lected maternal characteristics (age, parity, etc), and hospital of birth, excluding infants with intrauterine infections and major congenital malformations.^{151–155} Race is often used as a proxy for SES in inner-city populations. Hospital of birth may serve as a proxy for type and quality of perinatal care and area of residence, although high-risk mothers may be transported to tertiary perinatal centers from other areas of residence.

Because many early-childhood studies have not included birth controls, it may be necessary to find controls at school age.^{156–160} The most commonly used method is to randomly select a classmate of the same gender, race, and age (within 3–6 months) as the study child. The school serves as a proxy for area of residence and type and quality of education. Ideally, all the children of the same age in the child’s school, rather than class, should be considered as potential controls, because high-risk children repeat grades more often than low-risk children. When children are home-schooled, attend special schools for the disabled, or have moved out of the area, matches are usually selected from the school the child would have attended. Other study-design methods include random selection of controls from regional school-system records.^{158,161} Studies of large regional or national populations have obtained outcomes through linkage of birth records to school records^{162,163} or linkage of birth records to military-recruitment records^{164,165} with comparison of the subjects to the rest of the population.

Follow-up rates of at least 90% should be achieved at early childhood, at least 80% at early school age, and at least 70% at middle-school age and during adolescence.^{124,159} Follow-up rates of control subjects are usually 10% to 20% lower than those of study subjects. In addition, despite the best attempts, control subjects usually have subtly better home environments than study subjects. Intervention and control subjects who are lost to follow-up are usually of lower SES than those followed. Because there are higher rates of loss to follow-up among control lower-SES subjects, the controls are usually of higher SES than study subjects.^{166,167} Also, families of children considered healthy may be less likely to return. Therefore, it is imperative that strategies be developed to maintain compliance, because it is difficult to determine the “true” outcome of lost infants.

Elements needed to maintain good follow-up rates are:

1. Enrollment of subjects before discharge from hospital and identification of a specific contact person.
2. Multiple back-up addresses of family and place of work.
3. Postdischarge and interim visits during the first year of life, for clinical purposes of developmental and health surveillance, and maintenance of family involvement even when the first formal study visit may only be at 2 years of age; ideally, comprehensive health care should be provided but is usually not feasible.¹⁶⁸

4. Close communication with, and respect for, health care providers of the subjects.
5. A dedicated study coordinator who is prepared to track and call families at night and over weekends and a research staff prepared to accommodate parent work schedules and to work weekends and perform home visits if necessary.
6. Reimbursement for transportation and parking and specific financial incentives for time spent for the collection of study data.
7. Adequate funding for all of the above.

OBJECTIVE 5: DETERMINE ALTERNATE, LESS COSTLY METHODS AND APPROACHES FOR FOLLOW-UP AND THE ROLE OF THE COMMUNITY PHYSICIAN

Because of limited funding sources, it is currently not feasible for all NICUs to have a comprehensive follow-up program. NICUs that do not have the resources to establish a program need to share information with the family and primary provider about increased risk of neurodevelopmental, behavioral, growth, and medical sequelae and facilitate referrals to early intervention and/or a child development center. Clinical programs with limited funding available, however, may use screening methods such as a phone or in-house parent interview as a first-stage screen to determine if more in depth assessments are warranted or if referrals to early intervention or educational resources are indicated. In addition, a clinical program with limited resources may by necessity offer a single follow-up visit. An optimal assessment age combines a short interval between discharge and assessment age (to minimize tracking) with a developmental age at which the accurate diagnosis of motor and developmental handicaps is feasible. The approach should facilitate a timely diagnosis and referrals as needed for families and center surveillance objectives. The feasibility of collecting some annual well-defined short-term follow-up data for all NICUs continues to improve. The ability to provide feedback on individual child outcome and support for families is available to all NICUs.

The NICHD Network identified 18 to 22 months' corrected age as the optimal time for a single visit. Interim visits or phone contacts are recommended for tracking purposes.

Community physicians can take an active role participating in follow-up by performing periodic developmental screening and responding to requests for health information on a child who does not return to the follow-up program. This requires a partnership between the community physicians and the tertiary care center and the use of standardized tools. In addition, follow-up programs can provide valuable information about the child's growth, neurodevelopment, and behavior to the community physician.

Table 6 contrasts 4 levels of management for the individual provider, for programs with clinical surveillance or referral objectives, and for programs with combined research and clinical objectives. Whereas the clinical program may maintain a database with a limited number of key variables, screen children (an important service for families), and re-

fer, the research program has the opportunity to develop more sophisticated protocols that are hypothesis driven and explore novel assessments. Screening tools such as the Ages and Stages⁹² and CAT/CLAMS⁹³ may be administered during an office visit or over the phone. Primary care providers who perform a screen may share information with the follow-up or diagnostic program and refer families as needed. Diagnostic and/or follow-up programs reciprocate by sharing results of comprehensive evaluations and recommendations. Primary care physicians can collaborate by completing study forms requesting data on growth, medical status, vision, and hearing.

OBJECTIVE 6: DETERMINE THE CHALLENGES ENCOUNTERED IN MULTICENTER NETWORKS

Multicenter networks have the advantage of being able to assess low-incidence neonatal illness such as perinatal asphyxia and achieve adequate sample sizes for hypothesis-driven studies within a shorter period of time than a single-center study.^{169,170} However, a number of challenges must be addressed if a network is going to succeed:

1. Achieving standardization of study protocols, manuals, definitions, and methodology among centers in diverse geographic areas is a major challenge for networks. Multicenter networks vary in their approaches to planning well-coordinated follow-up studies.
2. Achieving adequate follow-up rates is a major challenge, particularly with populations having diverse SESs, cultures, and primary spoken languages. The NICHD network endorses a follow-up rate of at least 80% for centers at 18 and 30 months' corrected age.
3. A third challenge for multicenter networks is to define the critical study population and the interval for enrollment. Network centers may enroll infants with a birth weight of ≤ 1000 g annually and follow them for 18 months as a framework for multicenter trials. This approach facilitates on-going standardization of follow-up protocols and reliability among examiners. An alternate approach is to enroll children born ≤ 1000 g every 3 years and follow each cohort for 3 years. This approach has somewhat higher costs, follows children to preschool age, and has changing protocols consistent with the age assessed. Networks should identify their unique study populations with high illness severity and poor outcomes for additional study (eg, extracorporeal membrane oxygenation patients).
4. A fourth challenge is to identify and enroll an appropriate cost-effective control population.

The following 4 multicenter networks provide insights into the complexities of conducting multicenter follow-up studies.

Vermont Oxford Network

The Vermont Oxford Network is a nonprofit voluntary collaboration of NICUs dedicated to improv-

TABLE 6. Psychometric Properties of WeeFIM, Vineland, Battelle, and Pediatric Evaluation of Disability Inventory

	WeeFIM ⁹⁵	Battelle ⁹⁷	VABS ⁹⁶	PEDI ⁹⁸
Purpose	Discipline-free measure of performance of functional skills in children aged 6 mo to 8 y and children through adolescence with neurodevelopmental disabilities	Discriminative measure of developmental skills in children aged birth to 8 y	Descriptive measure of communication, daily living, socialization, and motor skills for children aged birth to 18 y, disabled and nondisabled	Discriminative measure of functional limitations in children aged 6 mo to 7.5 y
Domains	Self-care, mobility, cognition	Daily living (adaptive), motor, communication, cognitive, personal-social	Daily living skills, motor, communication, socialization	Motor, self-care, social
Reliability	Excellent test-retest and interrater reliability; equivalence reliability of telephone interview	Test-retest and interrater reliability good to excellent	Split half for domains and composite, excellent; test-retest reliability, good	Excellent test-retest and interrater reliability
Validity	Content validation by expert group; concurrent validity with VABS, Battelle, AAQ, and PEDI; total WeeFIM at kindergarten entry correlates with special-education resources	Excellent correlation with VABS and WeeFIM; concurrent validity and WISC-R	Excellent correlation with school-age IQ	Concurrent with Battelle and WeeFIM
Application	Measure of functional status at age 5.5 y in VLBW CryoROP cohort; 4-y outcome in multicenter surfactant comparison trials; functional goal-setting in children with cerebral palsy, spina bifida, and genetic and acquired disabilities	Normal and disabled preschooler in early intervention; children with developmental disabilities in early elementary school	Preschool and long-term outcome in VLBW children; use in developmental disabilities	Parent interview format for children with cerebral palsy; clinical evaluation after rhizotomy and traumatic brain injury
Administration time, min	20	45	30	45

WeeFIM indicates Functional Independence Measure for Children; PEDI, Pediatric Evaluation of Disability Inventory; VABS, Vineland Adaptive Behavior Scale; WISC-R, Wechsler Intelligence Scale for Children-Revised; AAQ, Amount of Assistance Questionnaire.

ing the quality and safety of medical care for newborn infants and their families through a coordinated program of clinical trials, research, education, and quality-improvement projects. Established in 1988, the network has grown to >400 member centers representing NICUs throughout the United States and 17 other countries. The network maintains a database of information about the care and short-term outcomes of VLBW infants. In 1998, the Vermont Oxford Network began to collect follow-up data for ELBW infants at 2 years of age. To participate, centers had to have a follow-up clinic, evaluate children until 2 years of age, and administer the BSID-II.

Canadian Neonatal Network

The Canadian Neonatal Network was developed in 1996. Data were prospectively collected by trained abstractors at 17 tertiary-level NICUs across Canada. This network has assessed variations in practice relative to outcome. As a result, more regionalized approaches to follow-up are in place in Canada. A follow-up network was developed in Quebec in 2001 with funds from the Fonds de la Recherche en Santé du Québec and included all infants already enrolled in 6 follow-up programs.

NICHD Research Follow-up Study

The NICHD Research Follow-up Study was initiated in 1993 and consists of 16 academic tertiary care centers. The primary study objective for the NICHD Follow-up Network is to track and successfully evaluate >80% of infants entered in to the generic database with birth weights of 401 to 1000 g born after January 1, 1993, and infants enrolled in clinical trials with neurodevelopment as an outcome. Currently, the network is conducting a pilot 30-month neurodevelopmental outcome study on infants enrolled in the glutamine trial. The network has an infrastructure that includes a steering committee, protocol review committee, study manuals, standardized definitions, training protocols, and a data-coordinating center. Annual workshops and regular conference calls and meetings facilitate communication, coordination, and standardization. The network has established standardized methods to assess growth, motor skills, cognitive skills, language and behavior, and strict criteria for annual certification of Bayley examiners and neurologic examiners. All network study interviews and assessments are available in English and Spanish. Studies and assessments are conducted by network investigators at the individual center and have resulted in numerous publications.

Centers for Disease Control and Prevention Network for Developmental Disabilities and Birth Defects: Surveillance System and Centers of Excellence

This national surveillance system under the National Center on Birth Defects and Developmental Disabilities was mandated by the Children's Health Act of 2000 and implemented in April, 2001. The mission is to prevent birth defects and developmental disabilities, pursue the causes and risk factors associated with defects, and promote wellness of

individuals living with a disability. It supports a public health approach to the prevention of birth defects with surveillance systems, epidemiologic studies, and prevention programs. An example of a successful population-based surveillance system operating continuously since 1968 is the Metropolitan Atlanta Congenital Defects Program. Success is maintained with intensive case ascertainment, a case registry, a surveillance laboratory, and professional training.

OBJECTIVE 7A. IDENTIFY GAPS IN KNOWLEDGE ABOUT HIGH-RISK SURVIVORS IN YOUNG ADULTHOOD

1. Do they attain the social/educational status of their parents, or do they demonstrate downward mobility (measured by comparing educational and occupational attainment, associated rating of prestige, and earning capacity)?
2. Can they live independently and support themselves?
3. Do they develop normal social and family relationships (measured by specific questionnaires and from their history of permanent personal relationships of marriage)?
4. Does catch-up growth occur in late adolescence?
5. What are the long-term metabolic and cardiovascular implications of growth failure in utero, neonatally, and during infancy and of catch-up growth during various time periods of childhood and adolescence?
6. What are the long-term health effects of chronic medical sequelae of prematurity (especially pulmonary, visual, and neurologic)?
7. Do they have higher rates of psychiatric disorders, substance abuse, contact with police, and incarceration?
8. Does the ADHD associated with prematurity persist into adulthood?
9. Are there intergenerational effects of high-risk birth, prematurity, and/or low birth weight, and, if so, is it possible to break the cycle?

OBJECTIVE 7B. FURTHER AREAS OF INVESTIGATION

The following areas of investigation with a potential to improve and optimize the outcomes of high-risk infants were identified. The recommendations were:

1. to propose hypothesis-driven studies and RCTs to identify the mechanisms that contribute to both injury and plasticity and recovery of the CNS, including animal and tissue studies
2. to identify the assessment strategies and schedules that are the most predictive of long-term outcomes and identify earlier surrogate markers for long-term outcomes
3. to determine the predictive value of neonatal imaging modalities in the prediction of neurodevelopmental outcome
4. to identify perinatal interventions that contribute to positive neurodevelopmental outcomes

5. to conduct population-based studies to determine the true societal burden of illness within a geographic region or a national sample (currently, the vast majority of studies report on subgroups of infants such as VLBW, ELBW, chronic lung disease, asphyxia, small for gestational age, etc); a geographic sample would include all infants born within a geographic region (such a study could ask questions regarding the total population of infants born within a specific time interval, in a specific region, and followed for a predetermined length of time)

OBJECTIVE 8: PROPOSE RESEARCH QUESTIONS

1. What are the mechanisms by which intrauterine/neonatal inflammation/cytokines and hypoxia ischemia produce CNS injury, and what are the effects on long-term outcome?
2. What are the mechanisms contributing to and the interventions that can further reduce the severity of chronic lung disease in ELBW infants?
3. Does stress and/or recurrent pain in the neonate result in permanent physiologic changes in response to pain?
4. What threshold of bilirubin and what duration of hyperbilirubinemia result in neurodevelopmental injury?
5. What modalities of resuscitation contribute to optimal neurodevelopmental outcome of ELBW infants?
6. What is the outcome of the macro premature infant (1500- to 2500-g birth weight)?
7. What is the impact of major congenital malformations and cardiac anomalies on outcome, and what are the effective perinatal interventions?
8. What are the neurodevelopmental and growth morbidities associated with monochorionic twin pregnancy and higher-order multiples?
9. What is the cost/benefit of follow-up care and assessment?
10. What is the impact of neonatal and postdischarge nutrition on early catch-up growth and developmental outcome?
11. What is the role of early calorie and protein intake and human milk on brain growth, and what are the long-term effects on cardiovascular and endocrine function disorder?
12. What is the impact of specific antenatal and neonatal interventions (magnesium sulfate, antenatal steroids, postnatal steroids, repeat doses of indomethacin antioxidants) on brain growth and function?
13. What is the impact of medical and/or surgical interventions for NEC on outcomes? What are the potential interventions to prevent NEC?
14. What are the neonatal neuroimaging techniques that best identify neurologic insult and predict neurologic and developmental outcome?
15. What are the genetic factors contributing to CNS morbidity and recovery? Is there a genomic vulnerability to injury?
16. What are the mechanisms by which an enriched environment contributes to plasticity? Are there critical periods for intervention?

17. What are the best screening tools for identification of infants at risk of adverse neurodevelopmental sequelae?
18. What are the best early surrogate markers for long-term neurodevelopmental disability?

Systematic long-term outcome studies of extremely premature or ELBW infants are indispensable for perinatologists and neonatologists: (1) outcome data facilitate informed decision-making in the NICU and the development of strategies for identifying infants at high risk for medical and neurodevelopmental sequelae; (2) families of infants identified as high risk may be guided to comprehensive follow-up and early intervention, and (3) morbidity rates may be used to estimate resources that society should be prepared to provide to optimize QOL of survivors and their families. Considerable challenges, however, secondary to limitations of staffing, costs, and expertise with assessments confront investigators performing long-term outcome studies and these challenges contribute to a paucity of high-quality outcome data. Limitations of many studies include small sample sizes, heterogeneity of cohorts, heterogeneity of methodology, limited information about both perinatal clinical practice and perinatal complications associated with long-term sequelae, and heterogeneity of specific neurodevelopmental assessments and age of outcome.

CONCLUSIONS

Although single-center studies may address some of these issues and answer important questions, multicenter research networks with standardized study manuals, protocols, and methods are needed for representative surveillance and clinical trials. It is hoped that this supplement provides information that will help follow-up program directors and primary care providers make choices about assessment protocols based on options provided and practical considerations.

Unfortunately, ELBW infants remain at increased risk of neurodevelopmental sequelae. Well-conducted multicenter trials, which include neurodevelopmental follow-up, continue to be the catalysts that allow investigators to identify the mechanisms that contribute to injury and recovery and the perinatal interventions that contribute to positive neurodevelopmental outcome.

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