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The HYdrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental (HYBRiD) outcomes study: protocol for a longitudinal cohort study

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Abstract

Background Bronchopulmonary dysplasia (BPD) affects up to half of extremely preterm infants, and is associated with adverse long-term respiratory, neurodevelopmental, and educational sequelae and costly health service and family economic outcomes. The NICHD Neonatal Research Network Hydrocortisone for Bronchopulmonary Dysplasia (BPD) Trial evaluated the efficacy and safety of hydrocortisone treatment to prevent BPD in high-risk infants. The trial enrolled 800 very preterm infants with respiratory failure and followed the participants until 2 years corrected age to assess safety of the trial intervention. Longer-term impacts of hydrocortisone exposure and severity of BPD on functional outcomes of high-risk infants remain unknown. The HYdrocortisone for BPD Respiratory and Developmental (HYBRiD) Outcomes Study extends follow-up of all surviving children enrolled in the Hydrocortisone for BPD Trial until early school age. It aims to characterize the childhood functional motor, cognitive, academic, and pulmonary outcomes of this large, well-phenotyped trial cohort.

Methods Parents of surviving trial participants complete telephone questionnaires when their children are 3 and 4 years corrected age. A single in-person study visit takes place at early school age (5 years, 0 months to 7 years, 11 months corrected age). Children undergo a multidimensional assessment of functional outcomes and parents complete a battery of questionnaires. In 5 of 19 participating centers, respiratory mechanics are evaluated with impulse oscillometry.

Discussion The HYBRiD Outcomes Study will be the largest and most comprehensive evaluation to date of the functional early school age outcomes of children with a history of severe neonatal lung disease and of children exposed to HC during infancy. This will substantially improve understanding of the longer-term implications of severe neonatal lung disease; provide data to facilitate the development of future randomized intervention trials in this

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population; and inform public policy by enhancing knowledge about school age resource requirements in children with a history of prematurity and lung disease.

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Keywords Bronchopulmonary dysplasia, Child behavior, Child development, Hydrocortisone, Neurodevelopment, Outcomes, Oscillometry, Prematurity

Background

Modern neonatal care has improved survival to discharge for extremely preterm infants in the United States to about 80% [1, 2]. However, surviving extremely preterm infants have high rates of bronchopulmonary dysplasia (BPD) and a spectrum of neurodevelopmental disabilities. When BPD is defined as a need for supplemental oxygen at 36 weeks postmenstrual age (PMA), the NICHD Neonatal Research Network (NRN) has reported that rates of BPD have increased over the past 20 years, concurrent with improved survival for extremely preterm infants [1, 2]. In 2008–2012, BPD was diagnosed in 45% of surviving infants at 36 weeks PMA [1]. By 2013–2018, BPD incidence had risen to nearly 50% of surviving infants born at 22–28 weeks of gestation [2]. The longer-term impact of BPD includes increased hospital readmissions during childhood, as well as long-term neurodevelopmental and pulmonary morbidity and adverse family economic impact [3–7].

Developmental outcomes of children with BPD

BPD is a consistent *independent* predictor of adverse neurodevelopmental outcomes in children born preterm. Adjusted odds of adverse outcomes at 5 years are 2.3 (95% CI 1.8-3.0) times higher among children with BPD than among those without BPD [8]. BPD is associated with poor motor performance on the Movement-Assessment Battery for Children (m-ABC) assessment at 5 years, which is a key component of the diagnosis of Developmental Coordination Disorder (DCD). A growing body of evidence demonstrates that BPD is associated with decreased cognitive skills as measured by intelligence quotient (IQ) at school age [9–13]. The Extremely Low Gestational Age Newborn (ELGAN) investigators has reported increased risk of cognitive, language, executive function, academic, and social skill delays among 10-year old children with BPD [12]. An Australian study of 2018 school age children published in 2024 demonstrated that respiratory outcomes (measured with spirometry) and neurodevelopment are associated with severity of BPD [13]. Nevertheless, there remain important knowledge gaps regarding how children with BPD function as they enter school, relationships between school age neurodevelopmental outcomes and early disease severity and management, and how these children can best be supported at home and in the community.

Respiratory outcomes of children with BPD

BPD is associated with adverse respiratory outcomes in childhood and early adulthood. These include severe medical sequelae such as tracheotomies, home ventilator support and high-cost emergency care or repeat hospital admissions requiring intensive care [5, 14, 15]. A meta-analysis of pulmonary function testing with spirometry in children born preterm with BPD, those born preterm without BPD, and children born at term demonstrated significantly decreased $\%FEV_1$ in those born preterm, with a further decrease in preterm born children with BPD [6]. Extremely preterm children with BPD have more coughing, respiratory medication use and hospitalizations, and increased impact of respiratory disease on family functioning, than those without BPD at 18–22 months CA [16]. In summary, both extreme prematurity and BPD are related to poor lung growth and respiratory outcomes in sick preterm infants. However, much remains to be learned about lung function of children with BPD, particularly as they enter school age.

Outcomes after postnatal steroid exposure

Complicating matters, the longer-term developmental and respiratory outcomes after neonatal steroid exposure are uncertain. Early postnatal dexamethasone is associated with increased risk for cerebral palsy (CP). Yet, decreased use of dexamethasone over time has not been associated with decreased rates of CP [17]. Furthermore, meta-regression demonstrates decreased risk of adverse outcome (death or CP) attributed to dexamethasone exposure as baseline risk for BPD increases [18]. Reports of *school-age* outcomes after neonatal dexamethasone exposure are generally small, single center cohort studies. These studies suggest that dexamethasone treatment of BPD is associated with decreased IQ, poor school performance, and increased rates of adverse motor outcomes [19, 20].

Because dexamethasone has a long biologic half-life, suppresses endogenous cortisol production, and disrupts the balance between mineralocorticoid and glucocorticoid in the brain, it may not be the optimal steroid for treatment of lung disease in preterm infants. Therefore,

HC has been explored as an alternative. A large multicenter RCT in France ($n=523$) reported no difference in the rate of survival without BPD when extremely preterm (<28 weeks gestation) infants were treated with low dose prophylactic HC for the first 10 days after birth [21]. A meta-analysis of 2-year outcomes in randomized trials of *early HC for the prevention of BPD* found no difference in rates of CP and a significant *increase* in survival without neurodevelopmental impairment (odd ratio 1.8; 95% confidence interval 1.2, 2.6; $p=0.003$) [22]. The NRN Hydrocortisone (HC) for BPD Trial initiated HC later – between 14 and 28 days after birth – and reported no difference in survival without moderate or severe BPD and no difference in survival without moderate or severe neurodevelopmental impairment at 2 years corrected age [23]. Importantly, there remains a paucity of data on follow-up beyond 2 years after neonatal HC use.

The HC for BPD Trial evaluated the efficacy and safety of a 10-day tapering course of HC, starting between 14 and 28 postnatal days, for the prevention of BPD in high-risk infants [23]. The trial enrolled 800 infants born<30 weeks of gestation with respiratory failure and followed the participants until 2 years corrected age (CA) to assess safety of the trial intervention. Primary trial results were published in 2022 [23]. The HYdrocortisone for BPD Respiratory and Developmental (HYBRiD) Outcomes Study is a follow-up study of this existing clinical trial cohort until school age. This cohort presents *a unique opportunity to assess the impact of HC exposure and severity of neonatal lung disease on childhood functional developmental and respiratory outcomes in this cohort.* Figure 1 depicts the conceptual framework for the HYBRiD Outcomes Study, which will address several critical knowledge gaps about school age outcomes children who had severe neonatal respiratory disease.

The HYBRiD Outcomes Study will describe the neurodevelopmental, learning, and functional pulmonary outcomes of a multicenter cohort of children with a history of neonatal respiratory failure. We will utilize a novel composite primary outcome of functional impairment and novel measures of respiratory status to characterize the outcomes of the study participants. This study will improve our understanding of the longer-term implications of severe neonatal lung disease, facilitate the development of future intervention trials in this population, and inform public policy by enhancing knowledge about resource requirements in these vulnerable children.

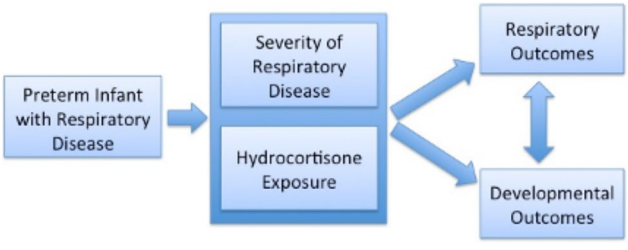

Fig. 1 Conceptual Framework for the HYBRiD Outcomes Study. The study will test the hypotheses that hydrocortisone exposure and severity of neonatal respiratory disease impact early school age functional developmental and respiratory outcomes and evaluate the relationships between these outcomes

Methods

Study aims

The objective of HYBRiD Outcomes Study is to characterize the early school age functional motor, cognitive, academic, and pulmonary outcomes of children with a history of neonatal respiratory disease, based on participation in the NRN HC for BPD Trial.

Primary study aims are to evaluate at early school age, in children enrolled in the NRN HC for BPD Trial:

i) The impact of hydrocortisone (HC) exposure on rates of functional neurodevelopmental and respiratory impairment.
ii) The relationship between severity of BPD and functional neurodevelopmental and respiratory impairment.

Secondary study aims are to assess at early school age, in children enrolled in the NRN HC for BPD Trial:

i) The associations between severity of BPD and behavior, executive function, adaptive skills, and quality of life.
ii) The impact of HC exposure on rates of Developmental Coordination Disorder (DCD).
iii) The relationships between functional respiratory outcomes and functional developmental outcomes.
iv) The validity of our novel functional respiratory outcomes (6MWT and ISAAC questionnaire) using impulse oscillometry (described below).

Design and setting

The HYBRiD Outcomes Study is a longitudinal cohort study that follows all surviving participants in the NRN HC for BPD Trial. The HC for BPD Trial was a masked, placebo-controlled randomized trial of the safety and efficacy of a 10-day tapering course of HC treatment for preterm infants who remained intubated at 14–28 days postnatal age [23]. Participants were followed throughout the neonatal hospitalization and evaluated at 2 years corrected age. Eight hundred infants were enrolled at 19 academic centers in the NICHD Neonatal Research Network (United States, full list of study sites available at clinicaltrials.gov).

In the HYBRiD Outcomes Study, families are contacted by phone (see detailed protocol below) when the children are 3 years and 4 years corrected age, and a final in-person study visit is conducted at early school age (Fig. 2). The school age visit was planned for 5 years corrected age with out of window visits permitted up to 7 years corrected age. However, recruitment was paused due to the COVID-19 pandemic necessitating extension of the follow-up window through (but not including) the date that the child turns 8 years corrected age. Ages are adjusted for prematurity to avoid bias in cognitive scores [8, 24–26]. All investigators, study staff, and participating families are blinded to exposure status. Families can request unblinding after completion of all study assessments.

Frequent contact is maintained with participating families until the final study visit is complete. This may include birthday cards, phone calls, emails/texts, or other approaches. The study teams communicate with families at least every 6 months and may do so more often if the family is at high risk for loss to follow-up. During tracking phone calls when children are 3- and 4-years CA, families complete a questionnaire about recent illnesses, hospitalizations, doctor visits, and respiratory symptoms. Respiratory symptom questions are based on the validated ISAAC questionnaire (see study measures).

Participants are scheduled for one in-person testing session between 5 years CA and 7 years, 11 months CA. *This is the key study visit*. Whenever possible, the assessment is scheduled after the child has entered

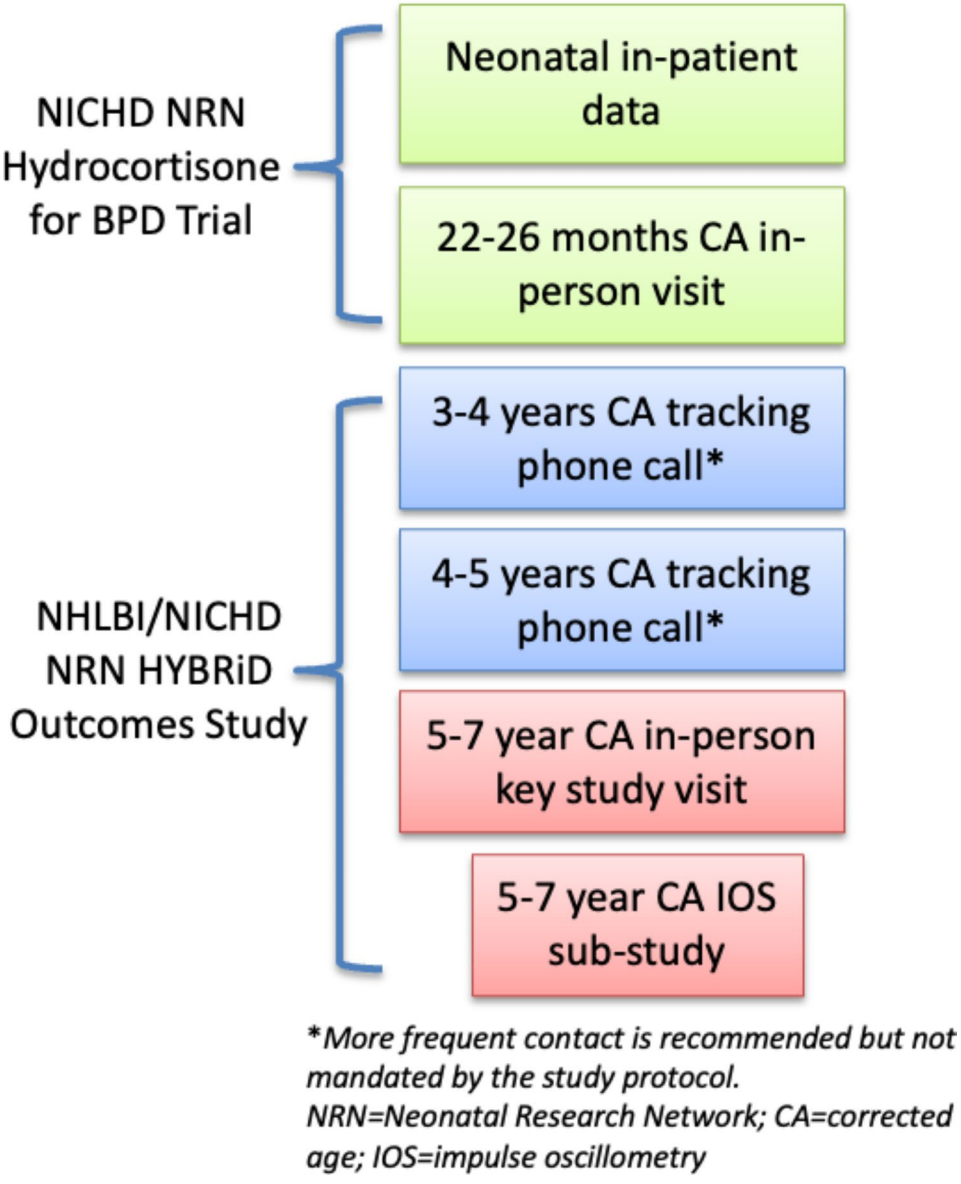

Fig. 2 Timeline of study data collection and assessments

kindergarten. The study assessments are scheduled at the convenience of the family, in the clinic or at home if necessary. Visits are arranged during school vacations and weekends when needed, and study teams travel to families who have moved > 200 miles from the study center or arrange for the family's travel. Impulse oscillometry (IOS) is performed in 5 of the 19 participating clinical centers. Centers participating in this portion of the study were selected because they enrolled well (> 50 participants) in the HC for BPD Trial and have local expertise in IOS. A full protocol for the IOS portion of the HYBRiD Outcomes Study, including recruitment and testing of full-term and healthy preterm control participants and details of IOS training, measures and quality control processes, is published elsewhere [27, 28]. For children unable to be seen for the key study visit, study personnel complete a loss to follow-up form. With parental permission, questionnaires are completed by telephone and whenever possible, results of school-based or other relevant assessments are submitted for review by the study adjudication committee.

Approval for the 3- and 4-year CA phone calls was obtained from each clinical center IRB as a modification to the primary HC for BPD Trial. The protocol for the early school age visit HYBRiD Outcomes Study assessment was then approved by each clinical center's IRB. The consent draft form was reviewed by the NRN Research Participants Subcommittee prior to submission to the IRB. Written, informed consent for the HYBRiD Outcomes Study was obtained prospectively at the 2-year follow-up visit or is obtained in person at the final visit, depending on local IRB permissions. Assent for study visits in 7-year-old participants (extended visit window due to COVID-19) was required by some participating center IRBs. The model consent form is available upon request from the DCC at RTI.

The HYBRiD Outcomes Study is conducted by a Clinical Coordinating Center (CCC) at Children's Hospital of Philadelphia and a Data Coordinating Center (DCC) at RTI, International. Members of the CCC and DCC, along with other members from the NICHD Neonatal Research Network, participate in the HYBRiD Outcomes Study Subcommittee, which meets at least quarterly to discuss study progress. When necessary, endpoints are adjudicated by members of the subcommittee with relevant expertise. The DCC manages communications all between the study subcommittee, sponsors, clinical sites, and other relevant parties.

Participants

All surviving children enrolled in the NRN HC for BPD Trial are eligible for the HYBRiD Outcomes Study. The HC for BPD trial enrolled 800 infants at 19 academic centers in the NICHD Neonatal Research Network (United States) after written, informed consent of parents. Inclusion criteria were: <30 weeks gestational age (GA), inborn or admitted to an NRN site within 72 h postnatal age, received at least 7 days of mechanical ventilation, and currently receiving mechanical ventilation. Exclusion criteria were major congenital anomalies, decision to limit support, indomethacin or ibuprofen treatment within 48 h, previous corticosteroid treatment for BPD, HC treatment for at least 14 days total or within 7 days of study start. Infants were randomized 1:1 to HC or placebo using a stratified, permuted block design with strata for GA (< and > 27 weeks) and center.

Measures

All study measures are listed in Table 1, along with estimated time for performing each measure. These are also briefly summarized below, with a focus on rational for the selection of each measure. Children who speak Spanish as a primary language are tested with a Spanish language speaking examiner.

Training and certification

Initial training of study teams (coordinators, neurologic examiners, and psychologists) was completed during a two-day workshop in Chicago, IL in September 2017. Each study psychologist then submitted a video of a full DAS-2 exam and self-critique for certification by a gold standard study examiner. Certified bilingual DAS examiners traveled to sites that did not have a local Spanish speaking examiner. One m-ABC examiner per site was also certified by sending a video and self-critique for review by a study gold standard examiner. Examiners were certified in the neurologic examination and 6-minute walk test by either attending the in-person training workshop or submitting a video for central review. Certified neurologic and m-ABC examiners were then permitted to certify additional examiners at their sites by reviewing materials, being observed, and then observing administration of these assessments. This is consistent with previously published NRN approaches to neurologic certification for the 2-year-old examination, which yields highly reliable results [29].

At the study midpoint, all DAS and m-ABC examiners underwent a pre-planned re-certification process. Because this timepoint fell during the COVID-19 pandemic, this was conducted via a virtual training workshop rather than a second cycle of video reviews. All study source documents re-reviewed centrally or by a second local person in order to monitor for both random and systematic administration or scoring errors [30].

Data and safety monitoring

The HYBRiD Outcomes Study protocol is being carried out in accordance with Office for Human Research

Table 1 Battery of assessments

Person Completing	Assessment Name	Measured Outcomes or Skills	Estimated Time (min)
Developmental and Neurologic Assessments			
Child	GMFCS and neurologic exam	Cerebral palsy	5–10
	Movement Assessment Battery for Children (m-ABC)	Gross motor and fine motor coordination	20–30
	Differential Ability Scales-II (DAS)	Cognition: verbal and nonverbal reasoning School readiness: colors, counting, letters, shapes, size/comparisons Visual-motor integration Working memory	30–45
Parent	Social Communication Questionnaire (SCQ)	Autism spectrum disorders	10
	Movement-ABC checklist	Impact of motor coordination on everyday function	5–10
	Adaptive Behavior Assessment System (ABAS3)	Adaptive function	15
	Child Behavior Checklist (CBCL)	Adaptive and problem behaviors	10–15
	Behavior Rating Inventory of Executive Function (BRIEF)	Executive function	15
	PedsQL	Quality of Life	5–10
	Services and activities questionnaire	Developmental supports, educational history, screen exposure, physical activity, and socioeconomic history	10
Respiratory and Medical Assessments			
Child	Physical exam, vital signs (including blood pressure and oxygen saturation) and growth	Current general medical and respiratory status	10
	6-minute walk test	Functional exercise capacity	6
	Impulse Oscillometry*	Lung mechanics: R5, Low frequency reactance area, and resonance frequency	15
Parent	ISAAC questionnaire and medical history	Resource utilization and respiratory symptoms	10

* Oscillometry is performed in 5 centers

Protections (OHRP) and National Institutes of Health guidelines and requirements. Oversight is provided by the Neonatal Research Network (NRN) Data Safety Monitoring Committee (DSMC). The NRN DSMC has representation from neonatology, bioethics, maternal-fetal medicine, and biostatistics. Expertise in neonatal respiratory physiology has been added to the DSMC for monitoring the HYBRiD Outcomes Study. In addition to monitoring safety data, the DSMC monitors enrollment, outcomes assessment, and attrition to ensure that the study will provide usable results with adequate statistical power. All communication with the DSMC funnels through the DCC. Prior to each planned (or ad hoc as necessary) meeting, the DCC reviews the study data, prepares interim reports, and arranges either an in-person meeting or teleconference to review these materials. Notification of DSMC recommendations to NRN Clinical Centers and NICHD/NHLBI are handled by the DCC. NICHD and NHLBI have the purview to act on DSMC recommendations to suspend or terminate the study should that become necessary for any reason. No specific stopping guidelines were planned a priori. The DSMC charter is available upon request from the DCC at RTI.

The HYBRiD DCC has a detailed quality management plan, outlining quality assurance procedures, specifications, audits, inspections, and other activities to ensure that the study meets applicable quality standards and regulatory requirements. The quality management plan was prepared in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) E6 and applicable federal regulations for clinical studies. Both off-site (centralized) and on-site monitoring is performed by DCC and CCC personnel as needed.

Data are collected via a centralized web-based electronic data capture (EDC) system developed by RTI and hosted on FISMA-Low secure servers, ensuring all data are transmitted via Hypertext Transfer Protocol Secure (HTTPS). EDC users are provided with role-based access, allowing them to key in and view only data appropriate for their site location and trial responsibilities. The EDC was programmed to include real-time queries, such as warning triggers for out-of-range values, logic errors, data comparisons, and missing data. The system allows users to key in coded values as documented on the trial case report forms. Data and unresolved queries are regularly reviewed by a clinical data manager, who assists site staff in resolving any issues.

Though anticipated to be infrequent, adverse events are monitored and reported per protocol guidelines. In the unlikely event of a serious adverse event (SAE) occurring at any of the clinical centers, it would be reported within 24 h of discovery to the NICHD Program Scientist (acting as medical monitor for all NRN studies), the DCC, and the DSMC as necessary (following established

and codified processes). Local Institutional Review Board (IRB) policy for reporting SAEs would also be followed.

Neuro-developmental assessments

The primary assessment of cognitive skills and intelligence in the HYBRiD Outcomes Study is the Differential Ability Scales-2 (DAS). The Global Conceptual Ability score of the DAS is strongly correlated with the full-scale intelligence quotient (IQ) score of the WISC-IV (correlation coefficient = 0.84) but is shorter to administer in this age range and includes a school readiness component, which is essential for assessment of functional outcomes [31]. Importantly, the DAS was normed with special attention to African American and Hispanic populations, which is particularly important for interpretation of language performance [32]. The DAS is increasingly used in school aged follow-up studies of large neonatal cohorts [33]. The DAS Early Years Cognitive Battery is appropriate for children from age 3:6–6:11; therefore it is ideal for testing 5 year olds at high risk for cognitive delay. The School Readiness and Working Memory diagnostic clusters of the DAS are ideal for assessment of risk for school delay (a component of the primary outcome) and problems with executive function. The DAS has a supplementary Spanish-language version, which is administered to children whose parents identify Spanish as their primary language.

Among children who have abnormal findings on neurologic exam, cerebral palsy is classified anatomically based on a hierarchical classification tree of cerebral palsy subtypes [34, 35]. Functional level is classified as per the Gross Motor Function Classification System [36–38]. Impairment of fine or gross motor coordination, or functional motor impairment, is defined based on the Movement Assessment Battery for Children (m-ABC) Total Impairment Score (TIS) < 5th percentile (severe motor coordination impairment) or 5th-14th percentile (moderate motor coordination impairment). The m-ABC is attempted for all children; however, in keeping with the diagnostic criteria for Developmental Coordination Disorder (DCD), abnormal motor coordination is only diagnosed in children who can participate fully in the m-ABC and do not have CP, blindness, or cognitive impairment (DAS Global Conceptual Ability < 70). Diagnosis of DCD also requires that the functional impact of the movement difficulty be assessed; thus, the m-ABC Checklist is completed by the parent.

Difficulties with behavior and attention are assessed with the Child Behavior Checklist (CBCL). An additional benefit of using the CBCL is that it was used in this cohort at 22–26 months corrected age, enabling an assessment of the trajectory of behavior and attention difficulties in the study population. We assess the presence of autism spectrum disorders with the Social Communication Questionnaire (SCQ) and quality of life with the Pediatric Quality of Life (PedsQL) inventory. Executive function is assessed with the working memory subtests of the DAS and the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire, which is completed by the child's parents. Parental report of adaptive behavior, which is how the child uses their skills in everyday contexts, is assessed with the Adaptive Behavior Assessment System-3 (ABAS). Additional parent questionnaires collect data about resource needs (therapy services and equipment needs), educational experiences and supports, screen time use, and physical activity.

Respiratory assessments

The Six Minute Walk Test (6MWT) is the primary measure of functional pulmonary outcomes in this study. The 6MWT directly assesses the participant's functional respiratory capacity by assessing exercise tolerance at the level required during daily physical activities. 6MWT is an alternate to the elaborate procedures required for formal exercise testing or spirometry which, in addition to being simpler to administer, is less likely to be confounded by developmental stage. A strength of the 6MWT is that it does not focus solely on pulmonary function per se, but rather assesses the whole subject, thereby capturing the functional impact of poor pulmonary function. The 6MWT captures the functional exercise capacity of several exercise related systems (pulmonary, cardiovascular, systemic and peripheral circulation, neurological and muscle metabolism). The 6MWT has good measurement properties: it is reliable in several diseases, pediatric normative ranges are described in several races, and it is standardized for children 4–11 years of age [39]. The 6MWT is responsive to therapeutic interventions in many diseases. Children with CP have a lower 6MWT than matched normal children at 5–12 years [40]. In children aged 4–18 years with mild-moderate cerebral palsy [levels I-III on the GMFCS], the 6MWT has excellent test-retest reliability of 0.81 [41]. 6MWT correlates with both strength and pulmonary function in preterm infants with and without BPD [42, 43]. The 6MWT is low cost because it does not require sophisticated equipment or highly trained personnel. This allows data derived from research using the 6MWT to be used easily in future studies and applied in diverse settings. Ultimately, from the family perspective, the relative contributions of cardiac and pulmonary disability to decreases in physical fitness and functional exercise tolerance may be less relevant than the overall functional impact in the child. The 6MWT is conducted according to the guidelines of the American Thoracic Society [44]. However, the 6MWT is administered on a 15-meter course, rather than the standard 30-meter course, because this is most easily accommodated in the clinics where study visits is conducted.

This ensures that administration of the 6MWT is standardized across sites.

Because the pathophysiology of BPD has significant overlap with that of asthma, we will use a simple questionnaire widely used for childhood asthma, developed by the International Study of Asthma and Allergies in Childhood (ISAAC) collaboration [45]. Wheeze is understood by parents and is robust to recall, irrespective of parental education or social class-occupation [46]. There is considerable face validity to the use of this instrument in the target population because of the substantial overlap between asthma related wheeze and the childhood physiology of BPD. The ISAAC questionnaire was developed for 6–7-year-olds but has since been used in older and younger children. Symptoms of wheeze are well described in children with BPD up to age 2 years [16], but less information is available about later years. In the United States, the ISAAC questionnaire has been used in 384 ex-preterms at age 8, who were found to have high rates of wheezing in the prior 12 months, especially if they had had BPD [47].

Impulse oscillometry (IOS) will be used to validate our feasible, low-cost functional measures of respiratory outcome. IOS is a noninvasive method to assess large and small airways obstruction that requires minimal patient cooperation. IOS uses sound waves to measure pulmonary mechanics during normal tidal breathing [48]. IOS correlates with spirometry and can be performed in children who are too young or otherwise developmentally incapable of performing spirometry. Furthermore, in a study of asthmatic children age 4–7 years, respiratory system resistance (Rrs) measured by IOS was superior to FEV1 measured with spirometry in predicting the probability of asthma exacerbations [49]. Thus, it is the optimal *direct* measure of lung capacity and function in this age group. Nevertheless, studies of IOS in early school age children with BPD to date have been limited to small, ($n<50$) mostly single-center studies [50–52]. Therefore, the current study will be a substantial contribution to understanding of IOS measures in young children with high risk for chronic respiratory morbidity related to prematurity.

Outcome definitions

The primary outcome of functional developmental impairment is a composite of several functional outcomes that can be measured directly in the child, and will be defined as *any one of* the following:

1) Cognitive delay: General cognitive ability (IQ) > 2 SD below the mean (i.e., < 70) on the DAS-II.
2) Motor delay: Cerebral palsy defined as Gross Motor Function Classification System Level 2 or higher or severe motor impairment measured as m-ABC Total Impairment Score < 5th percentile.
3) Academic delay: Early school skills > 2 SD below the mean (i.e., < 70) on the school readiness subtest of the DAS.
4) Poor functional exercise capacity based on the 6-minute walk test.

Secondary outcomes include the components of the primary outcome, developmental coordination disorder (measured with the m-ABC), behavior problems (measured with the CBCL), quality of life (measured with PedsQL inventory), executive function (measured with the BRIEF), adaptive skills (measured with the ABAS), impact of respiratory disease on daily life (measured with the ISAAC questionnaire and medical history), and impact of BPD on health services and family life. Planned outcomes of the IOS sub-study are described elsewhere [27, 28].

Analyses

Statistical analysis plan

To address primary aim 1 and secondary aim 2 (impact of HC exposure on outcomes), generalized linear mixed-effect models will be constructed using SAS PROC GLIMMIX or NLMIXED to compare school-age outcomes by HC exposure, controlling for gestational age and center, consistent with the primary trial analysis. The form of the model will be specified based on the distribution of the outcome measure. We will fit robust Poisson models of the primary outcome (functional developmental impairment) and secondary outcomes (cognitive, motor, and school delays and poor functional exercise capacity) included in the definition of functional impairment, and for developmental coordination disorder. In addition, we will compare the HC and placebo treatment arms based on scores on the outcome measures, using linear models for normally distributed outcomes (e.g., DAS-II conceptual ability scores) and cumulative logit models for ordinal outcomes (e.g., GMFCS level). Unadjusted and adjusted proportions and mean scores for the HC and placebo groups will be calculated for each outcome, as appropriate. These models will allow us to determine whether HC treatment is associated with better outcomes in these children.

Analyses for primary aim 2 and secondary aim 1 (relationship between severity of BPD and outcomes) will use similar generalized linear mixed-effect models. We will fit models of each outcome by severity of BPD [53, 54], controlling for gestational age, center and treatment. We will additionally test for an interaction between treatment and severity of BPD.

For secondary aim 3, we will fit generalized linear mixed effect models similar to those described above to

compare outcomes among children based on their performance on functional respiratory measures (i.e., 6-minute walk test, ISAAC questionnaire. For example, we will test whether distance on the 6-minute walk test is associated with higher cognitive scores.

Finally, for secondary aim 4, using data from the subgroup of participants receiving impulse oscillometry, we will examine the validity of the functional pulmonary assessments (6MWT and ISAAC questionnaire). We will compute Pearson and/or Spearman correlations between continuous scores on the functional assessments (6MWT scores, number of symptoms on ISAAC questionnaire) and the impulse oscillometry measurements (respiratory system resistance and reactance and frequency dependency of resistance) for all participants and then separately by HC treatment group. The type of correlation will be selected based on the distributions of the variables using results of a recent simulation study that describes the conditions under which each type of correlation performs optimally [55]. Moderate to high correlations ($r \geq 0.70$) between impulse oscillometry and the functional assessments would support the validity of the functional assessments. To further examine the validity of the ISAAC questionnaire, we will conduct t-tests to compare mean oscillometry measurements of children whose parents report they have versus do not have each symptom on the ISAAC questionnaire, and to compare children with any versus none of those symptoms. These analyses will allow us to determine whether the symptom items on the ISAAC questionnaire capture significant differences in respiratory functioning for this population.

All analyses by trial treatment group will include participants on an intent-to-treat basis. Impact of missingness will be assessed in separate sensitivity analyses.

Sample size and power estimates

The sample size for the HYBRiD Outcomes Study is dictated by the number of participants who were enrolled in the primary trial ($n=800$) and survived until early school age (approximate $n=720$). Based on prior NRN follow-up studies, we anticipate that about 80% of surviving children enrolled in the parent trial will be evaluated for this proposed follow-up study ($n=575$). To account for potential difficulty in recruitment of older children who are not currently being actively tracked at all sites and potential losses with changes to the composition of the NRN, we conservatively present power projections using 500 children or 250 on each arm.

Projected power for the HYBRiD Outcomes Study composite primary outcome of functional impairment is based on estimated event rates from the neonatal literature, because no study has assessed the same composite outcome and the current study population is expected to have higher morbidity than many existing trial or population-based cohorts [8, 56]. The Victorian Infant Collaborative Study reported "clinically important neurobehavioral impairment" (mild to major neurosensory, intellectual, educational, or *behavioral* impairment) in 55% of extremely low birth weight infants at 8 years [57]. Based on these data, we conservatively hypothesized that at least one component of the composite (functional motor, cognitive, academic, or respiratory impairment) will be present in about 50% of the placebo group. *Note that this assumption provides the most conservative estimate of power for this study.*

Assuming a two-tailed test with Type I error set at 5%, a sample size of 500 participants will provide ≥ 80% power to detect a difference of ≥ 13% in the risk of functional developmental impairments between the two treatment groups. This is a clinically meaningful difference in outcome rates, with 8 being the number needed to treat to prevent one child from having functional disability. This magnitude of difference is similar to the effect size noted for trials of high-risk populations in the meta-regression of the relationship between of dexamethasone exposure and death or cerebral palsy by Doyle, et al. [18]

In addition to the outcome of functional developmental impairment, we examined power for comparisons of functional respiratory outcomes (e.g., distance from 6-minute walk test). With $N=500$, we would have >80% power to detect differences in mean scores between the two treatment groups with a small-sized effect f expressed as the standard deviation of the means [58]. Specifically, we have >80% power to detect f=0.12 or higher, assuming the inclusion of 10 covariates accounting for 20% of the variation in the outcome. For the subgroup receiving impulse oscillometry ($N=100$), we would have >80% power to detect differences in mean values for impulse oscillometry between the two groups for medium-sized and larger effects (f=0.26 or higher).

Discussion

We planned the HYBRiD Outcomes Study to assess the impact of exposure to HC and BPD severity on the functional outcomes of extremely preterm-born children at early school age. There are several novel aspects of the planned study worthy of highlight. Five years of age is a critical time in childhood. This is the youngest age that children can participate in many assessments that require focused effort. This is also the earliest possible age of school entry, which makes it the ideal time to identify potential learning or developmental needs so that appropriate services can be provided prior to school failure.

In contrast to outcomes such as intelligence quotient (IQ), "functional" outcomes assess a child's ability to participate in everyday activities such as playground play and classroom learning. Functional outcomes measure the integration of behaviors or skills that allow the

child to achieve important everyday goals. Functional outcomes are patient and family centered because they are relevant in the context everyday life. Examples of functional outcomes are movement problems that interfere with participation and social interaction, managing everyday tasks such as tying shoes or using scissors appropriately, school/academic readiness, and exercise capacity. Functional outcomes are an important focus for the World Health Organization, school systems and special education programs [59]. The US Department of Education Office of Special Education Programs requires that states report the following three outcomes annually for preschool (age 3–5 years) children with Individualized Education Programs (IEPs): [1] Positive social-emotional skills; [2] Acquisition and use of knowledge and skills, including early literacy; and [3] Use of appropriate behaviors to meet their needs. This is in direct response to the Individuals with Disabilities Act, which states: "In conducting the evaluation, the local educational agency shall use a variety of assessment tools and strategies to gather relevant functional, developmental, and academic information, including information provided by the parent" [60]. Thus, the multidimensional construct of functional impairment that will be measured in the current study aligns completely with federal guidance about what data are relevant for understanding a child's strengths, limitations, and needs during early childhood [61].

Finally, school-age studies of respiratory outcomes in children with a history of BPD have primarily focused on spirometry, which is the gold standard criterion for measurement of childhood pulmonary function [62]. As described above, both prematurity and BPD are known to be associated with decreased pulmonary function throughout childhood and into early adulthood when measured with spirometry [6]. Spirometry requires special equipment and is best performed in tertiary care centers with specially trained staff. Because cooperation is required, spirometry is difficult to perform at 5 years, particularly when children have cognitive or behavioral limitations. For these reasons, data derived from existing studies have a high degree of selection bias and are not easily generalizable to other studies or populations. Furthermore, little is known about the relationships between pulmonary function as measured by spirometry and functional developmental or respiratory outcomes as children enter school age. Impulse oscillometry (IOS) is an alternate technique for assessment of pulmonary function that is effort independent. Therefore, it can be used at earlier ages and in children with developmental or behavioral disorders. However, such sophisticated techniques are difficult to use in large or population-based studies due to cost and limited availability. In the HYBRiD Outcomes Study, we will use IOS as an independent measure to validate two practical, functional measures that can be widely applied both clinically and in larger outcomes studies: the 6MWT and the ISAAC questionnaire. We will validate these novel outcomes concurrently with IOS in 5 centers and correlate these novel pulmonary outcomes with early school age developmental outcomes in our entire study population.

A comprehensive assessment of academic/school readiness, functional motor outcomes, behavior, and exercise tolerance such as the assessments that will be conducted in the HYBRiD Outcomes Study provides parents with a realistic picture of their child's potential strengths and challenges in everyday scenarios. It also allows schools and support institutions to devise meaningful treatment plans. In the proposed study, this functional assessment is critical to a better understanding of how severity of neonatal respiratory disease and HC exposure affect children's ability to engage at an age-appropriate level in multiple contexts. Importantly, this is the first study to assess both functional respiratory and developmental outcomes concurrently in a large cohort of children with a history of neonatal lung disease. Our tools are simple, feasible, and inexpensive. Therefore, results of this novel study can be easily generalized to future cohorts and can be used clinically. The results of our study may have important implications for public policy and resource planning for this vulnerable population of children.

In conclusion, it is critical to understand the effect of neonatal interventions such as HC treatment at least through the time that its impact on important, child- and family-centered outcomes can be assessed. The HYBRiD Outcomes Study will evaluate the trajectories of respiratory and developmental outcomes in a high-risk cohort of former extremely preterm infants through early school age. We will determine the associations between severity of neonatal lung disease and HC exposure and early school age respiratory and developmental outcomes. Furthermore, this will be the first large trial cohort to explore the interplay between respiratory outcomes and academic and cognitive outcomes as well as how these outcomes are related to quality of life and behavior in children with severe neonatal lung disease. The detailed data available from the NRN HC for BPD Trial, together with the HYBRiD Outcomes Study, will fill these critical knowledge gaps. These data may be used to better counsel parents about possible outcomes for their children, to select high-risk children for earlier developmental interventions and therapies, and to inform the design of future research about prevention or treatment of the adverse consequences of severe neonatal respiratory disease.

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Author contributions
All authors made substantial contributions to the design of the work and the acquisition, analysis, interpretation of data. All authors have read and approved the submitted version and have agreed to be personally accountable for their own contributions to the work. All authors agree to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. In addition, SD wrote the first and final drafts of the work submitted. The NHLBI Project Scientist and Clinical Trials Specialist serve as non-voting members of the HYBRiD Steering Committee and in this role provided scientific input on the final protocol design and study execution methods described in the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The HYBRiD Outcomes Study was approved by the local IRB at each participating center and written informed consent to participate was provided by a parent or legal guardian of each child.

Competing interests
The authors declare no competing interests.

IRB reference numbers for each participating center are:
Case Western Reserve University: FWA00004428, U Hosps Cleveland Med Ctr: FWA00003937, University of Texas Southwestern Med Ctr: FWA00005087, Wayne State U: FWA00002460, Emory U: FWA00005792, Cincinnati Children's Hosp Med Ctr: FWA00002988, Indiana University: FWA00003544, Women & Infants Hosp of Rhode Island: FWA00000056, Leland Stanford Junior U: FWA00000935, UAB Hospital: FWA00005960, The University of Texas Health Science Center at Houston: FWA00000667, Duke University: FWA 00009025, University of North Carolina at Chapel Hill: FWA00004801, WakeMed Health & Hospitals: FWA00000213, U of Iowa (The): FWA00003007, MercyOne Des Moines Medical Center: FWA00000046, University of Utah: FWA00003745, Intermountain Healthcare: FWA00007905, U of New Mexico HIth Sciences Ctr (UNMHSC) (aka): FWA00003255, University of Pennsylvania: FWA00004028, Children's Hosp of Philadelphia: FWA0000459, U of Rochester: FWA00009386, University at Buffalo - State University of New York: FWA00008824, U of California Los Angeles (UCLA): FWA00004642, Nationwide Children's Hosp: FWA00002860, The Children's Mercy Hospital: FWA00002496, Research Triangle Institute International LLC: FWA00003331.

Consent for publication
Not applicable. Results of the HYBRiD Outcomes Study will be shared at a major academic pediatric meeting and then submitted to a peer-reviewed medical journal as soon as possible after completion of the study. All members of the study subcommittee will be named as authors on the primary study publication, given their contributions throughout the conduct of the study, as long as they meet ICJME authorship criteria at the time of publication. No professional writers will be used. Results will also be shared with the families of study participants through a paper mail or e-mail study newsletter.

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