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Design and implementation of a multicenter protocol to obtain impulse oscillometry data in preterm children

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ABSTRACT

Importance: Objective measures of lung function are critical for assessing respiratory outcomes of prematurity. Among extremely low gestational age neonates (ELGANs) (< 29 weeks gestational age), high rates of neurodevelopmental impairment may interfere with lung function testing. Impulse oscillometry (IOS) is a noninvasive test of respiratory system mechanics not requiring forced expiration.

Objective: To describe a multicenter study design for respiratory follow-up testing in a cohort with a high rate of extreme prematurity.

Methods: School-age children enrolled in two prior trials of ELGANs and term controls were assessed by IOS at five centers. Groups consisted of children with prematurity with a high incidence of bronchopulmonary dysplasia, children with prematurity with no or minimal lung disease, and healthy term children. A rigorous centralized review process reviewed IOS studies for technical acceptability. Approach to design and implementation, rates of feasibility and success, and characteristics of participants are described.

Results: A total of 243 children were recruited, of whom 239 (98%) attempted oscillometry. There were high rates of technical acceptability across all three cohorts (85%–90% of attempted tests), and across all five centers (80%–94% of attempted tests). Respiratory and neuromotor clinical factors associated with testing failure included a higher number of days on ventilation during neonatal intensive care, a history of intraventricular hemorrhage grade 3 or 4, and gross motor functional impairment.

Interpretation: We report high rates of feasibility and success of oscillometry in a large multicenter ELGAN population, in whom neurological and developmental comorbidities likely play a confounding role.

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INTRODUCTION

Objective measures of lung function are critical for assessing respiratory outcomes of prematurity. Spirometry is the most frequently used tool for assessing pulmonary function;[1] however, testing children under 6 years of age can be challenging because spirometry requires the child to perform forced expiratory maneuvers.[2] Success of spirometry has been associated with age and school performance,[3] and is dependent on the developmental stage of the patient and his/her ability to perform adequate maneuvers.[1] Because cooperation is required, spirometry can be particularly difficult to perform when children have cognitive impairment or behavioral problems.

Among extremely low gestational age neonates (ELGANs) (< 29 weeks gestational age), high rates of neurodevelopmental impairment[4] could potentially prevent successful lung function testing. There is also a high incidence of bronchopulmonary dysplasia (BPD) in this cohort, with 49.8% of ELGAN infants in the same study meeting criteria for BPD based on continuous supplemental oxygen use at 36 weeks postmenstrual age.[4] BPD has been strongly associated with worse neurodevelopmental outcomes.[5] One testing method is respiratory oscillometry assessment, which assesses lung function during tidal breathing and does not require forced maneuvers. The subject breathes through a mouthpiece while pressure signals are applied.[6] The measured relationship between pressure and flow is used to calculate respiratory system mechanics.[6] Oscillometry has been used in preschool-aged children in clinical and research contexts.[7] These assessment tools have been used in cohorts of children born very (< 32 weeks of gestation) and extremely (22–28 weeks of gestation) preterm, with and without BPD.[8–12] A comparison of impulse oscillometry (IOS) to spirometry among 6-year-old children, including 88 children born extremely preterm and 84 term controls, demonstrated higher success rates for IOS than for spirometry, and correlation of the IOS variables resistance at 5 Hz (R5), the area under the reactance curve (AX) and the difference between resistance at 5 and 20 Hz (R5-20) to spirometry variables forced expiratory volume in 0.75 s ($FEV_{0.75}$) and $FEV_{0.75}$/forced vital capacity.[13]

Of the above studies referenced, all were single-center studies. Although multicenter studies incorporating oscillometry have been conducted in childhood asthma[14–16] and cystic fibrosis,[17] to our knowledge they have not been done in former ELGANs. Similar to Pryhuber et al.[18] in the published study protocol for the Prematurity and Respiratory Outcomes Program (PROP), we wished to describe a multicenter study design in a cohort with a high rate of extreme prematurity, with a focus on pulmonary function testing and its associated challenges.

This report describes the successful development and implementation of an ongoing multicenter IOS protocol, with 239 children tested to date. The stability of success metrics over time supports reporting an analysis of the feasibility of oscillometry testing in this cohort. Our objectives were to 1) describe a protocol for obtaining research-quality multicenter oscillometry data from preterm children, 2) describe the feasibility and success in obtaining research-quality multicenter oscillometry data from preterm children, and 3) report clinical features associated with failure to obtain research-quality data in the first 249 children eligible for this study. These findings should be helpful for any multicenter neonatal networks wishing to perform accurate and simple lung function follow-up.

METHODS

Ethical approval

All studies obtained institutional review boards approval at each participating center: Children's Hospital of Philadelphia (IRB 17-014247), Cincinnati Children's Hospital (IRB 2017-5335), Indiana University (1107006380), Children's Mercy Kansas City (17120725), and the University of Texas at Houston (HSC-MS-18-0248). A parent or legal guardian of each participant provided written informed consent. All study methods are carried out in accordance with relevant guidelines and regulations.

Study design

Two ongoing studies provided the opportunity to study early school-age pulmonary outcomes and oscillometry in very preterm-born children.

1. The Hydrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental (HYBRiD) Outcomes Study (NCT01353313) is a National Heart, Lung, and Blood Institute (NHLBI)-funded prospective follow-up study of the functional developmental and respiratory

outcomes of all surviving children who were randomized in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN)-funded Hydrocortisone for BPD Trial.[19,20] Subjects had a gestational age of < 30 weeks.
2. The Transfusion of Prematures Early School Age Follow-Up (TOP 5) Study (NCT01702805) is a prospective observational study that assesses long-term functional and neurological outcomes of extremely preterm infants enrolled in the TOP Trial.[21,22] Subjects had a birth weight ≤1000 g and gestational age 22–28 weeks. One hundred and twenty subjects with no BPD or Grade 1 BPD (using the 2019 NICHD definition)[23] were recruited to undergo respiratory assessment at early school age (for simplicity, this cohort is referred to as "Healthy Lungs Study - Preterm").

To contextualize lung function in these two cohorts of preterm-born children, we wished to have a comparison group with no history of prematurity or lung disease. Thus, the Healthy Lungs Two (HL2) study was designed.

3. The HL2: Respiratory Outcomes of Full Term Infants with Healthy Lungs study recruited 120 children born at ≥ 37 weeks between their 5th and 7th birthdays without histories of asthma, other breathing problems, cerebral palsy, or developmental or behavioral problems requiring an individualized education plan (IEP) or other management plan. For simplicity, this cohort is referred to as "Healthy Lungs - Term."

In summary, these recruited children fall into three groups (Figure 1):

- HYBRiD, children with prematurity and a high incidence of BPD;
- Healthy Lungs - Preterm, children with prematurity with no or Grade 1 BPD; and
- Healthy Lungs - Term, healthy children born at term.

The follow-up assessment was performed between the ages of 5 and 7 years, and corrected for prematurity when applicable. All participants were recruited from five NRN centers. Investigators at each site obtained institutional review board approval for all three studies. A parent or legal guardian provided written, informed consent for each participant.

Respiratory evaluation

All study participants were assessed with a 6-minute walk test (6MWT) and a respiratory and medical history questionnaire. These assessments capture the impact of disease on everyday function. The 6MWT serves as a direct functional measure of submaximal exercise capacity while providing integrated data on several physiologic systems (pulmonary, cardiovascular, neurological, and muscle metabolism).[24] The 6MWT was conducted according to the published guidelines from the American Thoracic Society. Because the pathophysiology of BPD has significant overlap with that of asthma,[25] the study used the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, which is widely used for large, multicenter cohort studies of childhood respiratory outcomes.

At five NRN centers, IOS was used to measure the resistive and elastic properties of the lung[7] to validate the two functional respiratory outcomes detailed above (6MWT and ISAAC questionnaire). Spirometry was not performed. These pulmonary outcomes will also be correlated with early school-age developmental outcomes of the HYBRiD and Healthy Lungs - Preterm participants, including cognitive, behavioral, motor, and school readiness measures. The five centers that participated in the IOS study were: Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Riley Hospital for Children at Indiana University, Children's Mercy Kansas City, and University of Texas at Houston. RTI International (Research Triangle Park) oversaw the protocol, the manual of procedures, and data collection forms, and provided all data management and analytic support for the studies.

The following sections describe the study investigators' approach to study startup, training, and quality control to ensure the collection of research-quality IOS data across centers.

Testing equipment

At all sites, oscillometry was performed with the Vyaire/CareFusion device, running through the SentrySuite program. On the day of testing, the device was calibrated and assessed via a test resistance and zero elastance.

Training and certification of examiners

To standardize testing, oscillometry was performed according to agreed-upon procedures modeled on the Childhood Asthma Research and Education (CARE) Network,[26–28] an NHLBI-funded 5-center network investigating childhood asthma. Technicians who had undergone required training performed IOS. Participating centers attended in-person training at the IOS Core in Indianapolis, IN. Prior to testing study subjects, each site submitted five trials to the supervising respiratory therapist for IOS site certification. Utilizing a "train the trainer" model, throughout the study period, individual site staff who performed the study evaluations completed 1 or 2 in-person training sessions with the local certified examiner. The first subject evaluation was then recorded and reviewed by the lead study examiner at the IOS Core for accuracy and reliability.

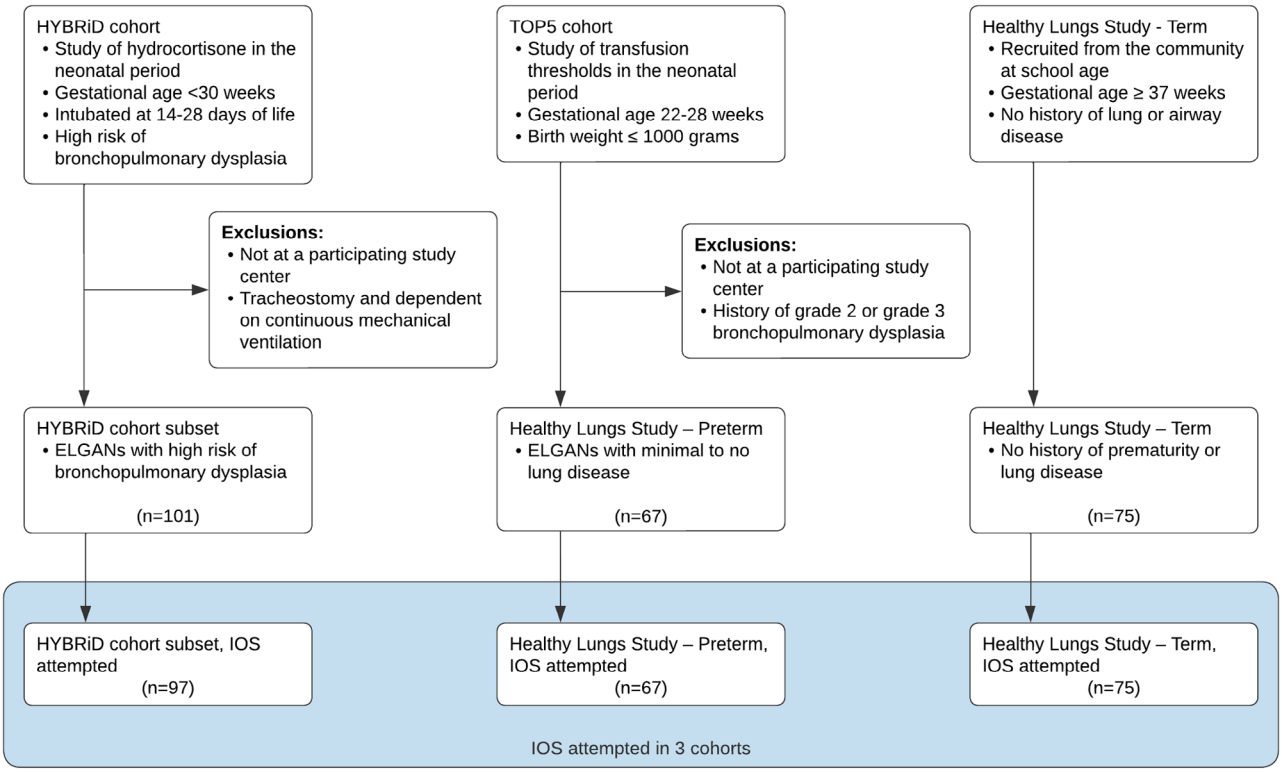

FIGURE 1 Recruitment of subjects for oscillometry. Goal enrollment of 200 children for Hydrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental (HYBRiD), 120 for Healthy Lungs - Preterm, and 120 for Healthy Lungs - Term. HYBRiD, Hydrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental Outcomes Study; TOP5, Transfusion of Prematures Early School Age Follow-Up Study; ELGANs, extremely low gestational age neonates; IOS, impulse oscillometry.

Order of administration

Follow-up visits included neurodevelopmental testing (in preterm cohorts), 6MWT, and IOS. There was variability across centers of the availability of the study team and proximity of the IOS equipment to the developmental testing area. However, centers were instructed to perform IOS prior to 6MWT when possible and to avoid performing IOS soon after the 6MWT, due to the theoretical possibility of exercise affecting pulmonary function measures. The order of administration was documented.

Subject technique

Testing was performed via mouthpiece interface, with subjects seated with upright posture, with the mouthpiece adjusted to achieve a "chin-up" head position. Nasal occlusion, mouth support, and cheek support were provided by research staff or a parent or guardian. A nasal clip could be used if it appropriately occluded the nose, and if preferred by the study subject. Subjects were coached by the examiner and research staff to achieve regular, tidal breathing, which was monitored by visual inspection and via the IOS software in real-time. Visual inspection of the lip seal around the mouthpiece and inspection of the volume-time tracing helped detect leaks. Cognitive impairment did not exclude subjects from IOS testing unless the subject was unable to perform an appropriate technique.

Successful strategies for producing high-quality test data included instructing the parent on technique so the parent could coach or demonstrate the technique (with their own mouthpiece), allowing the child to sit on the parent's lap for comfort (with appropriate adjustment of equipment), and refocusing the child by offering a small toy or book. For respiratory patterns, research staff monitored chest rise, provided breath-by-breath coaching, encouraged slower breaths, and used visualization techniques, e.g., relaxing on a beach or taking a nap. To avoid upper airway obstruction, strategies included repositioning the child to avoid slouching or neck flexion, listening for any vocalization to identify glottic closure, and describing breathing as "fogging a mirror" to encourage an open glottis. Some subjects required more than the software's default number of trials (10) to successfully produce an adequate number of high-quality trials.

Examiners reported observed errors in technique by noting on the test report which trials demonstrated leak (Figure 2),

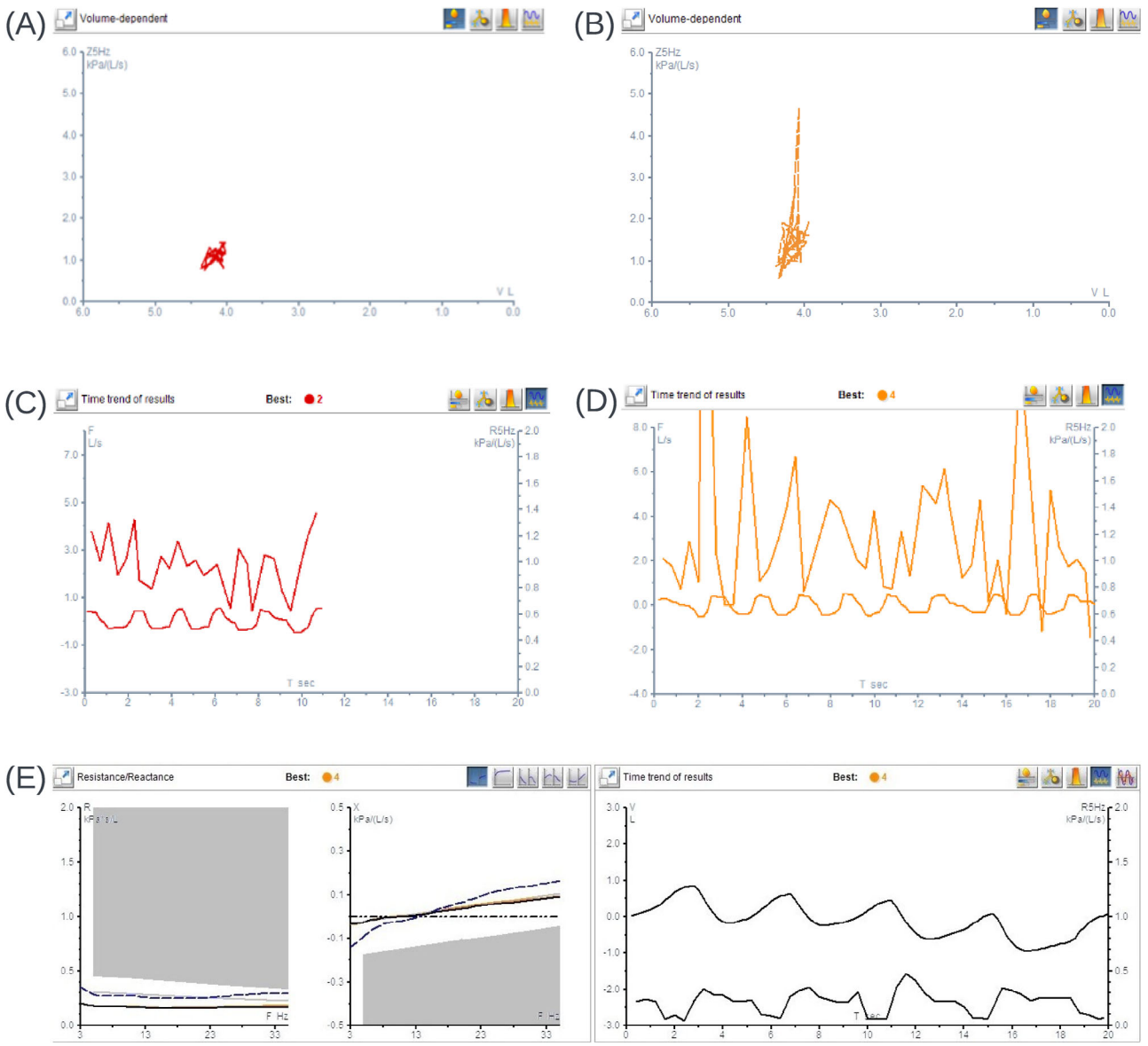

FIGURE 2 Impulse oscillometry tracings. (A, B) Impedance at 5 Hz (Z5), showing an acceptable trial (A), and an unacceptable trial (B) demonstrating a sudden increase in impedance. (C, D) Resistance at 5 Hz (R5), demonstrating an acceptable trial (C) and an unacceptable trial (D) due to intermittent large increases in resistance. This may be due to positioning or glottic closure. (E) Impulse oscillometry tracings for the leak at the mouthpiece. Dotted lines in the two left panels indicate measurements for resistance and reactance for trials without leaks. Solid lines indicate trials with the leak, that is, falsely low resistance and less negative reactance. In the right panel, the downward slope of the volume tracing indicates volume loss and leak.

cough, noise, or other evidence of glottic closure or obstruction to flow. These trials were excluded from subsequent analyses by the lead respiratory therapist at the IOS Core.

Quality control

All study source documents were reviewed locally and centrally to monitor for both random and systematic administration or scoring errors. The IOS reports were reviewed centrally by the lead respiratory therapist to verify that testing met five research quality criteria for acceptability, namely:

1. Visual observation of a regular respiratory pattern, leak-free, no cough or noise, no obstruction to flow or glottic closure;
2. Coherence at 5 Hz 0.6–0.9, coherence at 10 Hz ≥ 0.8;
3. 20 s of data collected (minimum 5 breaths);
4. Resistance at 10 Hz (R10) less than R5;
5. Reproducibility; three trials with R10 within 20% of the maximum measured R10 from trials meeting criteria 1–4.

These criteria were based on criteria used by the CARE Network for studies of oscillometry in pediatric asthma.[26–28] Study design and initial data collection

occurred prior to the 2020 European Respiratory Society task force report on technical standards for oscillometry, in which coherence evaluation was no longer recommended as a quality control measure.[29] Trials that did not meet the above criteria were excluded completely; due to limitations of the software, breath or artifact removal from a trial was not possible.

Data management

Raw forced oscillometry testing data from all five sites were uploaded to a secure server. Files were then reviewed by the lead respiratory therapist at the IOS Core, where the centralized overreading process was performed. The above quality control criteria were verified and an IOS quality report was completed. All raw data and research quality data are maintained by the Data Coordinating Center at RTI International. All testing data are de-identified.

Multicenter data review

Monthly virtual meetings were attended by study teams from all five centers, the data center, and NHLBI representatives. During these meetings, the investigators and respiratory therapists reviewed study progress, addressed challenges in data collection or study procedures, and discussed any unanticipated hurdles to ensure consistent protocol adherence across sites. For example, the coronavirus disease 2019 pandemic began after the study was underway. After robust group discussion, necessary adjustments were made to the device sanitizing process and use of personal protective equipment by participants and study staff to conform to infection control standards across all sites.

Technician and center feedback

The centralized IOS data quality review described above monitored individual centers for consistent errors or problems in technique. When problems were identified, the IOS Core staff met with the site's lead respiratory therapist and pulmonologist via videoconferencing to review errors and reasons why the tests were determined to be technically unacceptable. Strategies were recommended based on the common reasons for failure and included strategies for improving study-subject cooperation if applicable.

Assessment of success

For each subject, the research coordinator recorded whether the test was attempted, whether the testing was completed, and reasons that the test was not attempted if applicable. A test was considered attempted if the subject sat down at the testing device, even if no trials were produced. A test was complete if the subject completed 10 trials or at least 3 technically acceptable trials, as determined by the examiner. The three primary measures of interest for study quality control were:

Feasibility – The percentage of tests that were completed by the study subjects, out of the total number of tests attempted.

Success – The percentage of tests that were acceptable in accordance with the research quality criteria as determined by the central overreading process, out of the total number of tests completed.

"Real-world" success – The percentage of tests that met research quality criteria, out of the total number of tests attempted.

Statistical analyses

Each metric was calculated overall and separately by study and site. For IOS tests that did not meet the criteria for research quality data, we computed the percentage of tests that failed each criterion.

To compare the clinical characteristics of each cohort, chi-square tests were conducted for categorical variables. For continuous variables, *t*-tests were conducted for normally distributed variables, and median tests were conducted for all others.

Odds ratios (OR) were calculated to compare neonatal and school-age characteristics between cases where IOS tests were completed and acceptable and cases where the IOS tests were incomplete and/or unacceptable. Analyses were performed with SAS software, version 9.4 (SAS Institute), and $P < 0.05$ was considered significant.

RESULTS

Between June 2018 and December 2021, a parent or guardian provided consent for 243 children to participate in the three studies (HYBRiD, $n = 101$; Healthy Lungs – Preterm, $n = 67$, Healthy Lungs – Term, $n = 75$). Of these, oscillometry was attempted by 239 children (98%). Eligible children whose families did not consent to the IOS portion of testing were not included in the current analyses (4/105 children in HYBRiD, and 2/69 in the Healthy Lungs - Preterm group). As shown in Table 1, the cohorts differed by the expected variables based on inclusion criteria. By definition, term controls were required to have a gestational age at birth of 37 or greater weeks. HYBRiD participants had lower gestational age and weight at birth than the Healthy Lungs - Preterm participants. The HYBRiD cohort had a higher mean number of days on ventilation than the Healthy Lungs - Preterm cohort, as expected, since the Healthy Lungs - Preterm cohort excluded patients with grade 2 or grade 3 bronchopulmonary dysplasia. All

TABLE 1 Clinical features of the study cohort: children with caregiver consent for IOS ($n = 243$)

Variable	Term	Preterm		
	Healthy lungs - Term ($n = 75$)	Healthy lungs - Preterm ($n = 67$)	HYBRiD ($n = 101$)	*P*-value[†]
Sex				
Male	36 (48)	31 (46)	52 (51)	0.508
Female	39 (52)	36 (54)	49 (49)	
Race				
Black	8 (11)	39 (58)	45 (45)	0.254
White	56 (75)	26 (39)	51 (51)	
Other	10 (13)	1 (1)	2 (2)	
Unknown	1 (1)	1 (1)	3 (3)	
Gestational age (weeks)	–	25.7 ± 1.4	24.9 ± 1.5	<0.001
22–24	0 (0)	16 (24)	46 (46)	0.008
25–27	0 (0)	41 (61)	49 (49)	
28–29	0 (0)	10 (15)	6 (6)	
≥ 37	75 (100)	0 (0)	0 (0)	
Birth weight (g)	–	809.7 ± 133.3	730.0 ± 140.5	<0.001
Complications				
Intraventricular hemorrhage grade 3–4	–	6 (9)	21 (21)	0.041
Patent ductus arteriosus (PDA)	–	34 (51)	75 (74)	0.002
History of surgical PDA closure	–	6 (9)	20 (20)	0.057
Days on ventilation	–	3 (1–16)	43 (28–61)	<0.001
School-age follow-up				
Adjusted age at IOS testing (years)	6.0 (5.0–6.0)	6.0 (5.0–6.0)	6.0 (5.0–6.0)	0.189
Height (cm)	117.2 ± 7.0	115.7 ± 5.9	112.5 ± 6.1	<0.001
Weight (kg)	22.1 ± 4.1	22.4 ± 6.4	19.6 ± 3.5	<0.001
GMFCS level 2 or higher	–	3 (4)	10 (10)	0.201
Tobacco smoke exposure	1 (1)	11 (17)	23 (25)	0.222
Re-hospitalized in the past year (any cause)	–	2 (3)	4 (4)	0.679
Medications in the past year				
Inhaled bronchodilators for breathing problems	–	18 (27)	37 (40)	0.102
Inhaled steroids for breathing problems	–	9 (14)	26 (28)	0.032
Oral steroids for asthma or BPD	–	3 (5)	12 (13)	0.076
Oral medications other than steroids for asthma, allergies, or BPD	–	10 (15)	30 (32)	0.014
Anti-reflux medications	–	3 (5)	5 (5)	0.813
Anticonvulsants/seizure medications	–	2 (3)	5 (5)	0.477
Muscle tone relaxing or reducing medications or injections	–	1 (2)	5 (5)	0.208
High-calorie nutrition supplements	–	5 (8)	14 (15)	0.152
Treatment for a behavior problem	–	4 (6)	8 (9)	0.550

Data are presented as *n* (%) or mean ± standard deviation or median (interquartile range).

[†]Healthy Lungs - Preterm versus HYBRiD

Abbreviations: BPD, bronchopulmonary dysplasia; GMFCS, Gross Motor Function Classification System; IOS, impulse oscillometry; IVH, intraventricular hemorrhage; HYBRiD, Hydrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental Outcomes Study (children with prematurity and a high incidence of BPD).

Excludes two pilot cases conducted before IOS training. Birth weight, IVH, PDA, days on ventilation, GMFCS, re-hospitalizations, and medications were not collected for term children. Medical history data (smoking exposure, rehospitalization, and medications) were not available for 9 pre-term children.

TABLE 2 Feasibility and success rates in obtaining research quality data

Study/ Center	IOS expected† (a)	IOS attempted (b)	IOS attempted rate (b/a, %)	IOS Completed (c)	IOS completion rate (feasibility) (c/b, %)	IOS attempted and overread (d)	IOS completed and overread (e)	IOS overread and acceptable (f)	Technical acceptable (success) rate (f/e, %)	"Real-world" success rate (f/d, %)
Study										
HYBRiD	101	97	96	82	85	79	74	67	91	85
Healthy Lungs - Preterm	67	67	100	60	90	48	47	43	91	90
Healthy Lungs - Term	75	75	100	73	97	28	28	25	89	89
Total	243	239	98	215	90	155	149	135	91	87
Center										
A	57	57	100	51	89	18	18	17	94	94
B	22	22	100	19	86	21	19	19	100	90
C	53	51	96	46	90	30	30	24	80	80
D	84	84	100	76	90	68	64	59	92	87
E	27	25	93	23	92	18	18	16	89	89
Total	243	239	98	215	90	155	149	135	91	87

†IOS expected is the number of children whose caregivers consented to IOS.
Abbreviations: HYBRiD, Hydrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental Outcomes Study; IOS, impulse oscillometry.

preterm-born subjects had an adjusted age of 5 years or greater, in accordance with inclusion criteria.

There were high rates of real-world acceptability across all three cohorts and across all five centers (Table 2). The term controls had the highest rates of completing IOS testing, but overall acceptability rates were similar across cohorts. For children with a history of prematurity, there were similar rates of feasibility and success in the cohort with a high incidence of BPD (HYBRiD) compared to the cohort without significant lung disease (Healthy Lungs - Preterm).

The overreading process reported whether testing data met each criterion for technical acceptability (Table 3). The most common reasons that testing data did not meet technical acceptability were a failure to collect > 3 acceptable maneuvers or evidence of flow interruptions or airway closure on the flow tracing. No tests would have been excluded based on coherence alone. Rarely, a family consented to the IOS testing but the test was not attempted. The most common reasons for not attempting oscillometry testing were child refusal or behavioral problems (two of four subjects).

Next, we explored clinical factors associated with a lower likelihood of producing acceptable oscillometry data at early school age in ELGANs. Table 4 shows the clinical factors associated with testing failure, that is, the inability to complete the test or test data that were not technically acceptable. Significant factors associated with failure included respiratory and neuromotor characteristics. A higher number of days on ventilation during their neonatal intensive care unit course was associated with a higher rate of failure. Neuromotor factors associated with failure were

TABLE 3 Impulse oscillometry tests that did not meet criteria for research quality data: testing completed, but data did not pass quality checks ($n = 14$)

Variable	Not meeting criterion, *n* (%)
Acceptable tidal breathing	11 (79)
> 3 acceptable maneuvers collected	13 (93)
3 maneuvers with Coherence R10 > 0.80	9 (64)
20 s of data collected	5 (36)
Tracing free of flow interruptions/airway closure	13 (93)
R10 < R5 on acceptable maneuvers	6 (43)
Reproducibility; 3 trials with R10 within 20% of the maximum measured R10	8 (57)

Of the 14 unacceptable tests, 13 failed based on multiple criteria.
R10, resistance at 10 Hz; R5, resistance at 5 Hz.

TABLE 4 Clinical features associated with successfully obtaining research quality data: attempted impulse oscillometry (IOS) tests with completion and/or overreading data ($n = 143$) in the Hydrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental (HYBRiD) and Healthy Lungs - Preterm studies

Variable	Complete and acceptable ($n = 110$)	Incomplete and/or unacceptable ($n = 33$)	OR (95% CI)	*P*-value
Male	56 (51)	15 (45)	0.94 (0.48, 1.85)	0.861
Non-white	58 (53)	17 (52)	0.99 (0.50, 1.96)	0.978
Gestational age (weeks)	25.4 ± 1.5	25.2 ± 1.7	1.12 (0.86, 1.45)	0.396
22–24	35 (32)	13 (39)	0.90 (0.25, 3.29)	0.870
25–27	63 (57)	16 (48)	1.31 (0.37, 4.62)	0.672
28–29	12 (11)	4 (12)	REF	
Birth weight (g)	783.9 ± 141.4	726.0 ± 150.0	1.00 (1.00, 1.01)	0.046
Complications				
Intraventricular hemorrhage grade 3–4	14 (13)	10 (30)	0.34 (0.13, 0.85)	0.021
Patent ductus arteriosus (PDA)	70 (64)	21 (64)	1.00 (0.45, 2.25)	1.000
History of surgical PDA closure	16 (15)	7 (21)	0.63 (0.24, 1.70)	0.363
Days on ventilation	26 (6–44)	37 (14–60)	0.99 (0.97, 1.00)	0.022
School-age follow-up				
Age at IOS testing (years)	6 (5–6)	6 (5–6)	1.53 (0.82, 2.84)	0.182
GMFCS level 2 or higher	3 (3)	8 (24)	0.09 (0.02, 0.35)	<0.001
Tobacco smoke exposure	25 (24)	5 (17)	1.31 (0.47, 3.66)	0.607
Re-hospitalized in the past year (any cause)	4 (4)	0 (0)	N/A	N/A
Medications in the past year				
Inhaled bronchodilators for breathing problems	43 (41)	8 (27)	1.88 (0.77, 4.60)	0.169
Inhaled steroids for breathing problems	28 (26)	5 (17)	1.80 (0.63, 5.14)	0.276
Oral steroids for asthma or BPD	10 (9)	2 (7)	1.46 (0.30, 7.04)	0.639
Oral medications other than steroids for asthma, allergies, or BPD	32 (30)	7 (23)	1.42 (0.55, 3.65)	0.465
Anti-reflux medications	6 (6)	2 (7)	0.84 (0.16, 4.39)	0.836
Anticonvulsants/seizure medications	3 (3)	2 (7)	0.41 (0.07, 2.56)	0.339
Muscle tone relaxing or reducing medications or injections	2 (2)	3 (10)	0.17 (0.03, 1.09)	0.062
High-calorie nutrition supplements	14 (13)	4 (13)	0.99 (0.30, 3.26)	0.986
Treatment for a behavior problem	8 (8)	4 (13)	0.53 (0.15, 1.90)	0.330

Data are presented as *n* (%) or mean ± standard deviation or median (interquartile range).
Excludes 21 cases with completed IOS, but no data on acceptability (overreading). Medical history data (smoking exposure, rehospitalization, and medications) were not available for seven children. The odds ratio was not computed for rehospitalization due to empty cells.
Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; HYBRiD, Hydrocortisone for Bronchopulmonary Dysplasia Respiratory and Developmental Outcomes Study; IOS, impulse oscillometry; GMFCS, Gross Motor Function Classification System; N/A, not applicable; OR, odds ratio; REF, reference category.

a Gross Motor Classification Function System (GMCFS) score of 2–5 and intraventricular hemorrhage grade 3 or 4.[30]

DISCUSSION

There is limited understanding of the trajectory of lung health in former preterm infants in the current era of surfactant treatment, and further data are needed to characterize early lung disease in this population.[31–33] Neonatal care networks wishing to assess lung function follow-up studies in preterm patients who have been discharged from their neonatal intensive care units need to develop uniform guidelines across their network. In this study, we describe and implement such guidelines. Two ongoing studies provided an opportunity for the first multicenter study of lung

function at school age in ELGANs using IOS. The protocol described has generated high-quality data in children with a history of extreme prematurity, demonstrating the success and feasibility of multicenter oscillometry testing in this population, which is at high risk for neurodevelopmental conditions.

There are several multicenter oscillometry studies in healthy populations, most of which used preterm birth as an exclusion criterion or did not report rates of preterm birth in the study population.[15] Kattan et al.[14] assessed the acceptability of spirometry and IOS in a multicenter study of pediatric asthma and found high rates of acceptable test data (83.9% among 5-year-olds, with 90.2% attempting IOS). Ren et al.[17] performed FOT on a cohort of patients with cystic fibrosis at 36–60 months old across 5 sites, of which 79% of attempts produced research-quality data. Both studies excluded subjects with gestational age below 34 weeks. In the current study, despite the enrollment of children at higher risk for failure to acquire research-quality data, we have improved upon the success rates in prior studies. Possible reasons include rigorous in-person training at the study startup, continuous assessments of data quality, and monthly investigator meetings to identify and address unforeseen challenges.

Clinical factors associated with higher failure rates confirmed that sequelae of prematurity have a significant effect on the ability to produce research-quality data. Lower birth weight, more days on ventilation, and neuromotor comorbidities are associated with lower rates of success, and the potential for bias will need to be considered when analyzing oscillometry data. Thus far, we have had higher rates of feasibility in the cohort of children born at term, though success and real-world success rates have been similar to rates in the ELGAN cohorts. These were related to a lower attempted rate (perhaps due to a less motivated cohort), but a higher completion rate in the group born at full term. Thus, the challenges specific to assessing the lung function of the ELGAN population with IOS are not insurmountable when there is good coordination between centers and adherence to a prospective protocol.

Our study had a few limitations. The HYBRiD and TOP 5 study visit design may limit IOS success rates. These cohorts undergo comprehensive neurodevelopmental testing prior to performing oscillometry, whereas for term controls, oscillometry is the first assessment of the brief study visit. This may affect the ability of the child to follow directions and perform the periods of quiet breathing required for oscillometry. In addition, two of the five participating centers did not use oscillometry in clinical practice prior to the start of the study, while three centers were using it, albeit infrequently. This may affect inter-center success rates but would not be expected to result in differential success rates between preterm groups and the term group.

Our inclusion criteria for acceptance of testing trials outlined in the Methods section were rigorous. However, our data collection began in 2018, prior to the 2020 European Respiratory Society guidelines,[29] which excluded coherence as a measure. Other inclusion criteria were similar to current ERS guidelines and using the newer criteria likely would not have significantly changed our findings.

In conclusion, this is the first study of the feasibility and success of oscillometry in a large multi-center ELGAN population, in whom neurological and developmental comorbidities are likely to play a confounding role. We have shown that research-quality oscillometry data can be obtained in a high proportion of term and ELGAN children across five centers. This large sample of IOS results, with corresponding functional respiratory outcomes, will provide important insights into the pulmonary outcome of the ELGAN population at early school age. Characterizing clinical factors associated with a higher risk of failure provides insight into possible biases of such studies. The successes and challenges of the current study should help other neonatal follow-up networks successfully design and conduct future multicenter oscillometry studies in this high-risk population.

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CONFLICT OF INTEREST

Clement L. Ren – consultation to Vyaire. All other authors declare no conflict of interest.

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