Risks/Benefits. Specific aims include hypotheses you will investigate.

HYPOTHESES:
1) Airway resistance and airway inflammation can be accurately measured and tracked in toddlers and preschool children using methods such as airway resistance (Raw) and exhaled nitric oxide levels (FeNO);
2) These alternative methods correlate with validated spirometric values in older children;

OVERALL GOAL:
To assess the feasibility, the validity, and the reproducibility of different tools to measure pulmonary function in children 1-8 years of age, and to evaluate whether these tools are reproducible among two different centers: the University of Miami, a currently active National Children's Study, and St. Christopher's Hospital for Children in Philadelphia / Drexel University.

UTILITY AND RELEVANCE:
Raw and FeNO do not require patient cooperation beyond "normal" (tidal volume) breathing, and therefore can be performed in toddlers and preschool children. Meaningful measurements have been obtained in children as young as 2 years of age. These techniques should be easy to perform and reproduce in the research field. Both Raw and FeNO can be performed across the ages including older children and adolescents, and administering these tests requires relatively little expertise.
The relationship between measurements of resistance and flows is not well established. Simultaneous measurements of Raw, FeNO and subsequently spirometry (in children ~4-8yrs of age), will allow us to establish correlations between all three methods.
As part of the National Children's Study Vanguard phase, the current project will allow investigators to assess whether measurements of Raw and FeNO a) Can be performed in children younger than previously studied, b) Are correlated with each other, and c) Have a predictive value for lung function in later childhood and adolescence (as measured by FEV1 and other spirometric values).

AIMS:
1) To measure lung function in toddlers and pre-school children using Raw and FeNO, novel technologies that are accurate, reproducible, and easy to perform, and to assess whether such measurements are reproducible within each child and between two centers;
2) To assess the correlation between Raw, FeNO, and spirometry in older children (~4-8 yrs old);

SPECIFIC OBJECTIVES:
We will utilize technologies that have recently been developed to measure pulmonary function and airway resistance and to screen for airway inflammation; we will assess their correlation with standard spirometry in older children; and we will aim to extend their application to children of younger ages than previously studied. The primary aim of our study will be to determine whether airway resistance and exhaled nitric oxide can be measured reliably in children as young as 1 year, and to assess whether the results are comparable between different study centers. To this end, our study objectives are:

1. To recruit ~60-70 healthy children ages 1-8 years at each center.
2. To obtain the following measurements of lung function:
a. Conventional spirometry in all children 5 years or older, and attempt it in younger children who cooperate and can perform the required maneuvers (we anticipate ~4-8yrs of age).
b. Airway resistance (Raw) by the random occlusion technique (Rocc) in all participating children.
c. Exhaled nitric oxide (FeNO) in all participating children.
3. To assess the reproducibility of these tools by evaluating repeated measurements for each participating child during the study.
4. To assess the reliability of measurements by comparing the results between the two centers.
5. To assess the correlation between all three measures.
6. To assess parental perceptions of the testing and their likelihood to consent to the testing in the main NCS.
7. To identify technical or other issues that may arise during the study, in regards to the feasibility of using these technologies as a way to evaluate pulmonary function in young children.

4.2. * **Research Background**

Provide background and previous studies supporting the study rationale. Include a brief summary of existing knowledge relevant to the research. Explain how the research may contribute to the advancement of knowledge.

BACKGROUND AND SIGNIFICANCE:
Lung development continues at a remarkable pace from birth to about 6-7 years of age, and the lungs continue to grow until late adolescence. Understanding patterns of the progression of normal lung/2011

function in young children would allow clinicians to identify those with early changes in pulmonary function. Early changes in pulmonary function may indicate an increased risk of pulmonary disorders such as asthma or others. There are, however, limited longitudinal studies defining the range of normal development of the lungs from infancy.

One of the reasons for the paucity of studies and normative data on lung function in early childhood is that preschool children cannot perform conventional spirometry, the accepted standard for pulmonary function testing (PFT), which requires significant cooperation and coordination. Alternative techniques have gained popularity in recent years, such as studies of airway resistance (Raw) by the random occlusion technique (Rocc). Other techniques, such as exhaled nitric oxide (FeNO), measure the degree of inflammation in the airways.

4.3. **If you have cited references above, please attach a bibliography, including title, full author list, journal, date and pages. This bibliography should include only those articles referenced above.**

Name	Description	Version
There are no items to display		

4a. Description of Study (cont'd)

Rationale and Methodology

4.4. * **In non-technical, lay language, describe the study design and all study procedures, in order of sequence and timing. Include length of subject participation, what tasks are involved in the study, what tests or procedures subjects will be asked to complete or undergo, specific measures to be used, etc. If applicable, include frequency of visits, duration of visits, and study procedure calendar.**

This is a 2-center study (UM being the main site and Drexel/Philadelphia the secondary site). Each center will recruit ~60-70 children ages 1-8 years. Study visits will be as follows:

Visit 1: After consent/assent and initial evaluation by one of the study investigators, the parent/guardian will fill in a general health and respiratory questionnaire. Three different tools for pulmonary function tests (PFT) will be attempted with the child:
1) Airway resistance (Raw) by random occlusion technique (Rocc)
2) Exhaled nitric oxide (FeNO)
3) Conventional spirometry (for children approximately 4-8 years, if developmentally capable).

All three types of tests (Raw, FeNO, and spirometry) are standard approved techniques and procedures. Prior research on lung function testing has been done in children as young as 2-3 years of age. Raw and FeNO require only that the child breathe into a disposable mouthpiece for ~10 seconds (FeNO) or ~30 seconds (Raw). Conventional spirometry will only be attempted in children as young as ~4-5 years of age who can cooperate, as it involves following specific instructions such as taking a deep breath and exhaling quickly. None of these procedures are experimental, painful, or put their health or safety at risk. All instruments that will be utilized are FDA 501(k) cleared.

Visit 2 (approximately 1 week after visit 1): Attempts at Raw, FeNO, and if possible, spirometry (for children age ~4-8) will be repeated.

Visit 3 (approximately 1 month after visit 1): Raw, FeNO, and if possible, spirometry will be repeated. At this final visit there will be a survey regarding the family's perception of the ease of performing PFTs and their opinion on whether these are tools that could be used routinely in young children.

Follow-up: After finishing the study, we will perform one follow-up call at ~6 and at ~12 months from the initial study, using the follow-up questionnaire, to assess whether any of the study participants has developed asthma or other respiratory symptoms. There will be no study visits or procedures other than the phone call.

4.4.A. **Standard Measures:** Click the "Add" button to open the search window, then click the "Find"

button to browse and select measures.

Name of Measure	Brief Description	Type of Measure
There are no items to display		

NOTE: A copy of the first page of each standard measure is provided in the Library of Standard Measures for verification. Ensure that the version being used in this study is the same as the version that has been selected.

Upload any questionnaires and/or assessment tools to be used that are not listed above:

Name	Description	Version
Contact info sheet	Contact information. Detachable.	0.04
Health screen	To be used before each visit.	0.03
Main questionnaire	Main questionnaire. Visit 1.	0.03
Parental exit survey	Exit survey. Visit 3.	0.04
Phone follow-up questionnaire		0.01
Screening questionnaire		0.03
Study checklist		0.01

4.5. **Identify and distinguish between those procedures that are standard treatment versus those that are experimental/research-specific.**

☐ **Not applicable**

All three types of PFT (Raw, FeNO, and spirometry) are considered standard approved techniques and procedures. Prior research has been done in children as young as 2-3 years of age. We will be evaluating whether children as young as 1 year of age are able to cooperate and perform these studies. No experimental procedures will be utilized. All devices are FDA 501(k) cleared.

4.6. **Describe any therapeutic alternatives that may exist for the study population.**

☑ **Not applicable**

4b. Description of Study (cont'd)

Risk/Benefit Assessment

4.7. * **Describe the nature, degree, and if available, expected frequency of all potential economic/financial, legal, physical, psychological, social or other risks to which research participants may be exposed as a result of their participation in this research. If applicable, please describe the risk of investigational agents or devices (side effects).**

None of the 3 types of PFT utilized are invasive, nor do they pose any risk of physical harm to the participants. Two of them (Raw and FeNO) only involve the child breathing into the mouthpiece or face mask of the device for approximately 30 seconds. The third (spirometry) requires more collaboration in performing specific maneuvers and will be reserved to children over ~4-5 yrs of age (the standard age for clinical use of spirometry); of note, spirometry is standard of care in the diagnosis and management of pediatric respiratory diseases such as asthma, and both FeNO and Raw are increasingly utilized in clinical settings.

4.8. * **Are there potential direct benefits of this research to the subjects?**

◉ **Yes** ○ No

4.8.A. **If *yes*, provide a description of the potential direct benefits and indicate if all, or only some, of the subject groups may derive this potential benefit.**

While we will recruit healthy children, we do anticipate we might detect certain children with abnormal measurements. These children may have un-diagnosed asthma or other conditions and the detection of such conditions would be a direct benefit for the child. Additionally all families will meet with one of the study investigators, all pediatric pulmonologists, and will have the opportunity to ask questions about their child's respiratory health. Finally, families with identified smokers will be given information on the dangers of smoking and smoking cessation resources.

4.9. * **Are there potential benefits of this research to society?**

(●) **Yes** ( ) No

4.9.A. * **Please explain:**
The National Children Study (www.nationalchildrensstudy.gov) is an ambitious prospective cohort study that will examine the effects of environmental influences on the health and development of 100,000 children across the United States, following them from before birth until age 21. The goal of the Study is to improve the health and well-being of children.

Our project is one of the studies in the Vanguard or formative phase of the NCS. We aim to determine whether lung function can be measured much earlier (as early as 1 year of age) than conventional methods (usually 5 yrs of age). If these tools work we will be able to monitor lung function during the NCS and hopefully learn how to identify children at risk for respiratory disease much earlier in life than we currently are able to.

4.10. * **Explain why the risk/benefit ratio supports conducting this research.**
Risks from study procedures are minimal, and involve basically the child being unwilling to cooperate. All the child has to do is breathe into the instrument's mouthpiece for 20-30 seconds. Risks to privacy will be minimized by study protocol.

Direct benefits include education and possible detection of undiagnosed lung disease in some of the participating children. Indirect benefits will arise from the NCS, which will be the largest birth cohort study of children ever undertaken.

4c. Description of Study (cont'd)

Data

4.11. * **Describe follow-up, data storage methods, data security, authorized access to records and record retention, including site name and address.**
At each center, all study data (questionnaires and PFTs) will be collected using password-protected, FISMA-compliant laptops during study visits.

Data collected at UM will then be transferred to the password-protected desktop in the PI's office and entered into a database system with the capability to export files to statistical programs such as SAS or SPSS.

Data collected from the Drexel site will be uploaded to the PI's study desktop via a secure, FISMA-compliant VPN connection, and/or will be brought personally by that site's main investigator during site visits to UM, and will be merged with the main database.

All study forms and instruments will contain only the participant's Study ID. The only link between the patient's PHI (name and contact information) and the Study ID will be the Contact Information Sheet (CIS, attached, section 4.4.A). The CIS will not be duplicated or digitally backed up in any manner (ex. photocopies, digital scans, faxes, etc.) and will be stored in a secure, locked storage area or drawer within a secure location. CIS from the Philadelphia site will be either physically mailed to UM or will be handed to the PI in person during one of the study visits to UM.

Only the PI, co-investigators, and RA will have access to the study computers. These computers will be FISMA-compliant and located in the badge-accessible study/PI office. The master database will be only accessible to the PI until the end of the study. At that time, after de-identification has been verified and after data cleaning and verification, it will be accessible to the study co-investigators and the sponsoring institution. All original records will be kept according to UM's institutional policies.

4.12. * **Support the study validity by describing the statistical design, including quantitative and qualitative methods used to analyze data.**
This will be primarily a feasibility study to evaluate whether these PFT tools can be used in children younger than previously studied. We will assess this in the following ways:

1) Completion rate: Description of the rate of success in obtaining reliable measurements for each of the three tools (Rint, FeNO, spirometry).

2) Reproducibility: For each PFT, we will assess within-subject correlation among the 3 study visits (day 1, day ~5-10, day ~25-35).

3) Reliability: We will compare completion rates, reproducibility measures, and results between the

two centers, to assess whether these are measure that can be compared among multiple centers in the larger NCS.

4) Correlation: We will evaluate whether the results from three tools correlate with each other, to assess whether they can be used as 'surrogates' for each other in the larger NCS.

Privacy /Confidentiality Agreements

4.13. **Describe any privacy agreements or certificates of confidentiality, if applicable.**

4d. Description of Study (cont'd)

Deception

4.14. * **Is the use of deception part of the study design?**

○ Yes ◉ **No**

If *yes*, please answer the following 3 questions:

4.14.A. **Describe in detail the nature of the deception and explain why this is necessary for the research.**

4.14.B. **State how, when, and by whom the research subjects will be debriefed.**

4.14.C. **Upload a copy of the debriefing script.**

5. Study Participants

Per 45 CFR 46, human subjects (participants) means a living individual about whom an investigator (whether professional or student) conducting research obtains:

1. data through intervention or interaction with the individual; or
2. identifiable private information (i.e. pathological specimens, medical records, etc.)

5.1. * **Participant Age:**

Check all that apply		Notes
☑	0-6	*Parent Permission/Consent required for each participant*
☑	7-17	*Parent Permission/Consent & Child Assent required for each participant*
☐	18-65	*Consent required for each participant unless a waiver of consent is approved by the IRB*
☐	65+	*Consent required for each participant unless a waiver of consent is approved by the IRB*

5.2. **For the following questions, please use integers for your responses. For any question that is not applicable, please enter the number *0*.**
(Do not enter commas, decimal points or special characters)

5.2.A. * **Maximum number of subjects in the Protocol to be *screened* at all sites (regardless of PI):**
500

5.2.B. * **Total number of subjects in the Protocol to be *studied* at all sites(regardless of PI):**
200

University of Miami

5.2.C. * **Maximum number of subjects to be *screened* by this PI at *UM*:**
250

* **Maximum number of subjects to be *enrolled* by this PI *at UM*:**

100

*** From the above, how many are expected to *complete* this study (participate in the study beyond initial enrollment?**
80

Jackson Health Systems

5.2.D. *** Maximum number of subjects to be *screened* by this PI at *Jackson Health Systems (JHS):***
0

*** Maximum number of subjects to be *enrolled* by this PI *at Jackson Health Systems (JHS)*:**
0

*** From the above, how many are expected to *complete* this study (participate in the study beyond initial enrollment)?**
0

Miami VA Medical Center

5.2.E. *** Maximum number of subjects to be *screened* by this PI at *Miami VA Medical Center*:**
0

*** Maximum number of subjects to be *enrolled* by this PI at *Miami VA Medical Center*:**
0

*** From the above, how many are expected to *complete* this study (participate in the study beyond initial enrollment)?**
0

5a. Study Populations

5.3. *** Study populations to be included in this study where PI will be conducting research and those sites where the UM IRB will have oversight responsibility:**

Check all that apply	Notes
Normal, healthy volunteers	
Children/minors (under 18 years of age)	

5.3.A. **If *other*, please specify:**

5.3.B. **Describe below any additional safeguards that have been included to protect vulnerable subjects:**
None of the study procedures involve more than minimal risk for the participating children. Written informed consent will be obtained from the parents and assent from the children when age-appropriate.

5b. Inclusions/Exclusions

5.4. *** Is the population being enrolled in this study at high risk for incarceration?**
○ Yes ◉ **No**

5.4.A. **If *yes*, will the subjects be withdrawn from the study once they are incarcerated?**
○ Yes ○ No

5.4.A.(i) **If the above answer (question 5.4.A.) is *no*, describe how re-contacting/re-consenting, treatment, and/or follow-up will occur:**

NOTE: *If a subject becomes incarcerated while enrolled in a study, all research interactions and*

interventions with that subject, and the obtaining of identifiable private information about the subject, must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol.

If notified that a previously enrolled research subject has become a prisoner, the principal investigator must promptly seek IRB re-review of the protocol in accordance with the requirements of subpart C if the principal investigator wishes to have the prisoner-subject continue to participate in the research. ***In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.***

5.5. * **What are the criteria for exclusion of participants from the research?**

1) Diagnosed asthma
2) History of preterm birth before 34 weeks gestational age
3) Cystic fibrosis, chronic lung disease or other significant pulmonary disease
4) Recent acute respiratory tract infection (<2 weeks)*
5) Other acute or chronic disease at the discretion of the investigators

[*May be re-approached at a later time]

5.6. * **Will any population be systematically excluded in this study?**

○ Yes ◉ **No**

5.6.A. **If *yes*, provide rationale/justification for this exclusion:**

5.7. * **What are the criteria for inclusion of participants in the research?**

1) Ages 12 months to 8 years (inclusive)
2) Ability to understand and follow instructions
3) Willingness to participate and sign informed consent
4) Ability and willingness to participate in all 3 study visits

5.8. * **Will only one group of individuals be systematically selected and recruited for this study (e.g., welfare patients, racial and/or ethnic minorities, persons confined to institutions or persons determined to be incapacitated)?**

○ Yes ◉ **No**

5.8.A. **If *yes*, please state how this participant group will benefit from the results of the research and provide the reasons and justifications to target this group:**

5f. Research Involving Minors

* **Pick ONE category below:**

Select one

◉ **§46.404 Research not involving greater than minimal risk.**
HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that: