The Challenges of Evaluating Cross-Age Response to Asthma Treatment:

Insights from the NHLBI Asthma Network

Prepared for the 2014 theme issue in the Journal of Allergy and Clinical Immunology

Michael D. Cabana[1], MD, MPH
Susan J. Kunselman[2], MA
Sharmilee Nyenhuis[3], MD
Michael E. Wechsler[4], MD, MMSc

From the [1]Departments of Pediatrics, Epidemiology and Biostatistics and the Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco (UCSF), San Francisco, CA; [2]Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA; [3]Division of Pulmonary, Critical Care, Sleep and Allergy, University of Illinois at Chicago; Chicago, IL. [4]Department of Medicine, National Jewish Health, Denver, CO.

Correspondence to: Michael D. Cabana, MD, MPH
University of California, San Francisco (UCSF) Laurel Heights Campus
3333 California Street, Suite 245
San Francisco, CA 94118

E-mail Address: michael.cabana@ucsf.edu

Phone: 415-514-2660

Word Count: 4652 (abstract, 142)

Acknowledgement Support for this work was from the National Institutes of Health (HL098115). This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 TR000004. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

ABBREVIATIONS

ACRN	Asthma Clinical Research Network
ACT	Asthma Control Test
ACQ	Asthma Control Questionnaire
ASUI	Asthma Symptom Utility Index
BARD	"Best African-American Response to Asthma Drugs" Study
BID	*bis in die* (twice a day)
cACT	Childhood Asthma Control Test
CARE	Childhood Asthma Research and Education
COPD	Chronic Obstructive Pulmonary Disease
FDA	Federal Drug Administration
FEV_1	Forced Expiratory Volume at 1 second
FP	Fluticasone Propionate
HPA	Hypothalamic-pituitary-adrenal
ICS	Inhaled corticosteroid
IRB	Institutional Review Board
IU	International Units
LABA	Long-acting beta-agonist
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart Lung and Blood Institute
PACD	Pediatric Asthma Caregiver Diary
PASDS	Pediatric Asthma Symptom Diary Scale
SABA	Short-acting beta-agonist
VIDA	"Vitamin D add-on therapy enhances corticosteroid responsiveness in Asthma" Study
QOL	Quality of Life

KEY WORDS

Asthma

Clinical Trials

Study Design

Outcome Measures

Participant Recruitment

Pediatric Consent

Pediatric Assent

ABSTRACT

Clinical asthma studies across different age groups, or 'cross-age' studies, can potentially offer insight into the similarities, differences and relationships between childhood and adult asthma. The National Institutes of Health Asthma Research Network (AsthmaNet) is unique and innovative in that it has merged pediatric and adult asthma research into one clinical research network. This combination enhances scientific exchange between pediatric and adult asthma investigators and encourages the application of 'cross-age' studies that involve participants from multiple age groups who are generally not studied together. The experience from AsthmaNet in the development of 'cross-age' protocols highlights some of the issues in the evaluation of cross-age research in asthma. The aim of this review is to summarize these challenges, including the selection of parallel, cross-age clinical interventions, identification of appropriate controls, measurement of meaningful clinical outcomes, as well as various ethical and logistical issues.

INTRODUCTION

Asthma is characterized by multiple phenotypes and affects patients of all ages. Most asthma clinical trials focus on one specific age group. 'Cross age' studies, which recruit participants from multiple age groups not normally studied together, can potentially offer insight into differences in the diagnosis, treatment and management of asthma in infants, children, adolescents, adults and the elderly. In addition, these 'cross –age' studies can provide additional clues regarding the natural course of asthma phenotypes.

A fundamental question is whether asthma is the same in adults and children. It is not clear if the pathophysiology and response to asthma therapy is similar across ages. In addition, patients from different age groups may respond differently to predisposing features (e.g. viruses vs. allergies) of asthma. Also, children have not benefited as extensively from advances in drug development compared to adults; newer therapies are often not initially studied in the pediatric age group. This gap has resulted in many commonly used pediatric drugs without Federal Drug Administration (FDA) -approved indications for use in children (1). Without pediatric data, children are at risk by inappropriate extrapolation of data from adult studies when asthma medications are used off-label (2).

'Cross-age' studies can fill potential gaps in our knowledge of asthma management for specific age groups and identify common, as well as unique features of the disease across different age groups. Asthma is often recognized as a syndrome with common elements, but also heterogeneous phenotypes. As a result, it is important to develop more precise diagnostic, treatment and management strategies based on phenotypic and genotypic features (3). In all age groups, there is a need for novel approaches to prevent exacerbations, to manage step-down care

and to escalate care when asthma is poorly controlled (4, 5). There are similar needs for biomarkers that can identify different phenotypes of asthma in both adults and in children.

The AsthmaNet Experience with Cross-Age Protocols: VIDA and BARD

In 2008, to address these gaps, the National Institutes of Health, National Heart Lung and Blood Institute (NHLBI) issued a funding opportunity announcement to establish the NHLBI Asthma Network (AsthmaNet), as two other NHLBI networks, the Childhood Asthma Research and Education (CARE) Network and Asthma Clinical Research Network (ACRN), were concluding. This new NHLBI asthma network would be unique in merging the conduct of pediatric and adult asthma research into one network, would enhance scientific exchange between pediatric and adult asthma investigators as well as encourage 'cross-age' studies regarding similarities, differences, and relationships between childhood and adult asthma (6).

AsthmaNet has developed several protocols that were initially designed as cross-age studies (7). Two study protocols highlighted throughout this review include the "Vitamin D add-on therapy enhances corticosteroid responsiveness in Asthma" (VIDA) Study and the "Best African-American Response to Asthma Drugs" (BARD) Study. The VIDA protocol was eventually modified and initiated with only a focus on adult patients. Despite the inherent challenges in doing 'cross age' studies (reviewed below), and with the experience from the VIDA trial, the network developed its first cross-age protocol in the BARD study. Brief summaries of VIDA and BARD are included below.

The VIDA Study is a randomized, parallel group trial designed to assess if the addition of a l 28 week treatment with high dose vitamin D is superior to placebo in reducing asthma treatment failures for vitamin D insufficient (<30 ng/ml) individuals 18 years and older with persistent asthma who remain symptomatic despite low-dose inhaled corticosteroid therapy. The vitamin D

dose is a 100,000 IU load followed by 4,000 IU/day. The analysis will assess if the addition of vitamin D reduces the likelihood of treatment failure when compared to placebo. Given the high prevalence of both vitamin D insufficiency and asthma, the VIDA Study has the potential to impact daily asthma management.

The BARD Study is a 'cross-age' study designed to evaluate the best step-up long-term control therapy for participants of African-American descent with asthma, aged 5 years and older, who are inadequately controlled on low-dose ICS. It has been noted that African-Americans suffer a disproportionate burden of asthma morbidity compared to Caucasians (8, 9). A possible explanation for such racial disparities in asthma is that African-Americans respond differently to asthma therapies. For example, for African-American patients, there are reports suggesting a differential effect of add-on long-acting beta-agonist (LABA) treatment when asthma is inadequately controlled on low doses of ICS, compared to the results of studies of add-on LABA therapy with other populations (10, 11).

The BARD study design is a 66 week prospective, randomized, double-blind, crossover trial for African-Americans with asthma aged 12 years and above, and separately, in African-American children aged 5-11 years with asthma. Participants enter a run-in phase on low dose ICS. If symptoms are inadequately controlled, then participants are randomized to have their ICS dose increased and/or have a LABA added, with each participant receiving four different add-on treatments over the course of the follow-up period via the cross-over design. In both groups the study will examine, as a primary question, the efficacy of increasing the dose of ICS with or without the addition of a LABA. The BARD analysis will also compare the response of the pediatric and adult groups to these step-up therapies.

CHALLENGES WITH CROSS-AGE STUDIES

During the development of VIDA, BARD and other protocols, the AsthmaNet encountered and addressed various challenges in study design, including the selection of study interventions, appropriate controls, and meaningful clinical outcomes, as well as ethical and logistical issues in cross-age studies (**Table 1**) which are detailed below.

Recruitment Considerations

Clinical trial recruitment is a challenge in all age groups and recruitment strategies may differ across the ages. Children are the most racially and ethnically diverse group in the United States (12). For 'cross-age' trials involving children and diverse populations, it is necessary to include recruitment materials and methods, as well as assessment tools that are not only developmentally appropriate, but also culturally and linguistically appropriate (13). Specific strategies have been associated with the effective recruitment and retention of minority research participants (14). Ethnic and cultural background has been shown to affect perceptions of disease, understanding of disease and even perception of pulmonary function (15).

Recruitment for 'cross-age' studies should be age-appropriate, as well as culturally appropriate. With the ubiquitous use of new electronic media and mobile technology, there is increasing acceptability in the use of text-messaging, social networking and e-mail by patients to use electronic media to receive asthma information (16). In addition to traditional methods (e.g., physician referrals, patient lists and posted advertisements) (17), adolescents and young adults may be more accessible for recruitment through the Internet (18), social networking (19) or text-messaging. For the BARD Study, AsthmaNet sites use strategies that feature a variety of electronic media strategies (e.g., Internet postings, as well as the use of Facebook, Twitter and Google advertisements).

Consent and Assent for Cross-Age Studies

Research participants should understand the risks, benefits, alternatives and rights associated with involvement in a clinical trial (20). For 'cross-age' studies that include pediatric participants, the degree of participant involvement in the consent process is more complex.

With few exceptions, children do not have the legal capacity to give consent for their participation in research. Instead, informed permission from one parent or guardian is required. For those studies with greater than minimal risk, some Institutional Review Boards (IRBs) may require permission from both parents. In addition, for older children, assent of the child, as well as parental permission may be required. Assent includes a child's agreement to participate in a research study, as well as ensuring the child participant has a developmentally appropriate awareness of the study (21). As a result, 'cross-age' studies require a variety of forms for consent and assent, with different signature requirements. In addition to signed consent from all adult participants, the BARD protocol requires parent or legal guardian consent for participants between 5 and 18 years of age. Signed assent is obtained for participants 12 to 18 years of age and for those participants 5 to 11 years of age, if required by an institution's IRB.

Maintaining the Consistency of Study Interventions in Cross-Age Studies

In cross-age studies it may not be possible to maintain identical study interventions for all study participants, especially in trials focused on asthma medications. Although all medications need to be weight and age adjusted, additional modifications to study interventions may still be needed due to potential side effects, dosing issues, as well as drug availability issues.

For example, the BARD study included cross-over phases with medium-dose ICS and high-dose ICS, both with and without LABA. The interventions in the BARD protocol were modified in the pediatric arms due to concerns related to use of high dose ICS unique to children (22). Use of daily ICS in children is associated with a risk of suppression of growth velocity and effects on final adult height (23). In addition, the high dose ranges (500 mcg FP BID) described in the NAEPP guidelines are based on thresholds for potential systemic effects such as hypothalamic-pituitary-adrenal axis suppression and osteoporosis from sustained long-term use (24, 25).

As a result, for the pediatric and non-pediatric groups, the final BARD protocol was not identical in terms of ICS dosing. Both age groups utilize an ICS dose escalation; however, the pediatric population starts at only half the dose to be initiated in the older age group and escalates to a maximum that is half the dose of the non-pediatric population (**Table 2**). The protocol did not start the pediatric participants at 100 mcg BID during the run-in phase because this initial dose would result in an eventual maximum dose of 500 mcg BID that was considered to be unacceptable due to safety concerns. The step-up in the pediatric age group is a 2-fold increase in ICS (from 1xICS, 50 mcg BID, to 2 x ICS, 100 BID), whereas in the older age group, the first step up is a 2.5-fold increase (from 1 x ICS, 100 mcg BID, to 2.5 x ICS, 250 mcg BID). Despite the issues in dosing, the BARD protocol is able to maintain some symmetry between the studies for pediatric and non-pediatric populations, as both cohorts receive increasing doses of ICS with and without LABA.

There are other modifications that had to occur in the BARD protocol to accommodate the cross-age comparison and design. In the BARD protocol, for pediatric patients, the LABA is not “added-on” to the lowest dose of ICS, but rather to the next dose of ICS (at 100

mcg BID versus 50 mcg BID). This modification was pursued due to lack of a matching placebo inhaler (and potential concerns of utilizing two separate inhalers in children). While this creates some differences in the two groups, the analysis can still accommodate and answer the primary and secondary research questions.

Constraints in the Use of Placebo Controls in Children

A placebo control is often used as a key component in the evaluation of a new therapy in a randomized controlled trial. The need for a placebo is especially important for conditions such as asthma, where there is the potential for a high rate of placebo response, which may lead to an over-estimation of the effectiveness of an intervention (26). Although an alternative, non-placebo therapy potentially can be used for the control group, the effect size may be diminished. With a smaller effect size, greater numbers of subjects may be necessary, which increases a study's cost and complexity (27).

The use of placebo controls in clinical trials involving children, who are a vulnerable population, leads to even greater scrutiny (28). The Declaration of Helsinki, which outlines international standards for the ethics of clinical trials, states that every patient in a clinical study, including those in a control group, should be assured of the care consistent with the best proven methods when a standard of care exists (29). Without providing this standard of care (e.g., control group patients receiving placebo when a known effective asthma treatment exists), participants would be exposed to unnecessary risk and potential harm. For example, the clinical value of daily inhaled corticosteroid therapy for persistent asthma is well-established. A clinical trial assessing the effectiveness of a new treatment for persistent asthma with a placebo control (instead of a commonly-used ICS as control) would be ethically questionable (30). Professional

organizations, such as the American Academy of Pediatrics, have outlined conditions under which placebos may be ethically used in pediatric clinical trials (**Table 3**).

The efficacy of vitamin D therapy for prevention of asthma exacerbations is not known. As a result, for the VIDA Study, the use of a placebo would have been justifiable in reference to the potential prevention of asthma exacerbations. However, the VIDA Study assesses the efficacy of vitamin D for those patients who were vitamin D insufficient (<30 ng/ml). The inclusion of pediatric participants in this study was problematic, not in relation to asthma, but in relation to bone and development issues. Although adults may be able to tolerate temporary periods of low vitamin D levels, the effects of vitamin D for bone growth are well-established (31), as vitamin D is crucial for bone development, calcium homeostasis and many metabolic processes in growing children and adolescents (32). As a result, the use of placebo for children with documented low levels of vitamin D was not acceptable.

Current guidelines recommend that children non-deficient in vitamin D receive 400 IU of vitamin D per day. Although it potentially would have been possible to include pediatric participants and use 400 IU of vitamin D as a control in the VIDA Study, there would have been a study design tradeoff. The difference in dose between the intervention and control doses would have been decreased by tenfold (4,000 IU versus 400 IU). As a result, using this dose as a control could potentially decrease the opportunity to detect an effect from the intervention, or require the recruitment of a much larger sample size (27).

Maintaining the Consistency of Outcomes and Variables in Cross Age Studies

The consistent measurement of clinical outcomes is necessary to answer the questions being addressed in a clinical trial. However, in 'cross-age' studies it may not feasible or valid to collect such outcome measures in an identical manner. Different instruments may

need to be used for different age groups. The measurement of asthma control, exacerbation, symptoms and quality of life (QOL) are examples of this issue in 'cross-age' studies.

Asthma Control

NAEPP Guidelines highlight asthma control as a major goal of therapy and a patient's level of asthma control is a key factor in guidelines for how clinicians should modify their management of the disease (33). Ideally, in cross-age studies, it would be most efficient and simplest to use an instrument that has been developed for patients of all ages (e.g., Royal College of Physicians Three Questions (34); Lara Asthma Symptom Scale (35)); however, there is limited information on the validity, reliability and diversity of populations tested for these instruments.

The ACQ and ACT are commonly used instruments to assess asthma control; however, they are only applicable to older children. There are limited options for measuring asthma control in pediatrics. The Childhood ACT (c-ACT) instrument can be applied to participants 4 to 11 years, but there is limited data about how to assess the minimal clinically important difference for c-ACT values, as well as the responsiveness of the c-ACT over time (36). Given the limited options, the ACT and c-ACT were selected to measure asthma control for the BARD Study.

Asthma Exacerbations

A reduction of asthma exacerbations is one of the main goals of asthma treatment as defined by practice guidelines for asthma and, thus, a targeted outcome for clinical trials (33). Despite the importance of measuring asthma exacerbations in clinical trials, there has

been little consensus on the definition of an asthma exacerbation. Differences in how exacerbations are identified across-ages bring further complexity to the definition.

When possible, it is helpful for children to self-report their health (37); and it is suggested that children as young as 7 years of age can report their own asthma symptoms (38). However, in many cases, reports of asthma symptoms or exacerbations in children are dependent on the perception of a parent or caregiver, and the identification of symptoms by the caregiver may be dependent on their education level as well as their personality. For this reason, some of the most widely used definitions of exacerbations include one or more of these three components, all related to treatment, rather than symptoms: (i) systemic use of corticosteroids, (ii) asthma-specific emergency department visits or hospitalizations, and (iii) use of SABAs as quick relief medications (39).

The need to standardize asthma outcomes cross-ages for clinical trials has led to a recommended standard definition of asthma exacerbations: "a worsening of asthma requiring the use of systemic corticosteroids (or increase in the use of systemic corticosteroids) to prevent a serious outcome" (39). Although not part of the definition, detailed aspects including asthma-specific emergency department visits, hospitalizations, intensive care unit admissions/intubations and deaths should be reported when classifying exacerbations.

As one of the outcomes of BARD includes time to first asthma exacerbation, the above definition, use of systemic corticosteroids, has been chosen to define an asthma exacerbation across ages in this study. Finally, it is also important to note that in young children with asthma, exacerbations may be more frequent than in adults, possibly because of the frequency of viral infections and allergen exposures. A standard reporting form should be

developed to capture information related to precipitating factors of the exacerbation in the clinical trial setting.

Asthma Symptoms

The respiratory symptoms of asthma (episodic breathlessness, cough, wheeze, phlegm/mucus production and chest tightness) are used to assess the impact of patient-centered interventions. A common way to measure asthma symptoms has been to have patients or caregivers report their symptoms using paper or electronic daily diaries or retrospective questionnaires. Issues with these tools include recall and/or recall bias with the retrospective questionnaires and reliability with the daily diaries (40). Furthermore, the reliability of questionnaires and daily diaries in the pediatric population are varied, especially when the parent or caregiver and not the child completes them, as underreporting of symptoms may occur.

Despite the importance of symptoms to patient-centered research questions, there are only a small number of asthma symptom instruments that have undergone a validity assessment. These include two daily diaries in the pediatric population (PACD and PASDS), and one diary (Daytime Symptoms Diary) and one retrospective questionnaire (ASUI) in adults (40). The minimal clinically important differences have not been established for these instruments, and studies were conducted in a limited number of patient populations. Thus, the development of cross-age tools to measure symptoms is needed, especially in racial and ethnic minority populations to be more generalizable.

The AsthmaNet experience thus far has included the use of the retrospective questionnaire, ASUI, in the VIDA Study. As a large minority population has been recruited

for this study, it will be important to see if there are differences noted in the use of this tool. As there are no cross-age tools for symptoms, the BARD Study will be using both electronic daily diaries and questionnaires at study visits to assess symptoms.

Asthma-related Quality of Life

The inclusion of QOL as a clinical trial outcome recognizes the importance of understanding of the impact of the disease beyond symptoms or health care utilization. For example, asthma control or frequency of asthma symptoms may or may not be directly correlated with the impact of the disease on a patient's perceived QOL. There are many types of instruments that have been developed purportedly measuring QOL, but most do not do so; they tend to focus on measuring symptoms and activity/functional assessments rather than the patient's perception of the impact of asthma on a study participant's quality of life (i.e., asthma-related QOL) (41)). QOL is not merely the limitation on desired activities or health status, although these may be constructs included within QOL.

It is challenging to measure QOL in children and it is not appropriate to simply apply adult-based QOL instruments to children. If possible, children should contribute information about QOL directly (42); however, for young children, QOL information may need to be obtained from a proxy, such as a parent. In addition, there are a limited number of QOL instruments that have been validated and tested in a pediatric population comparable to the study population (41).

As a result, for 'cross-age' studies, a variety of QOL instruments may need to be used. In the BARD study, three different instruments were required. These included the Asthma Quality of Life Questionnaire (AQLQ+12) for participants 12 years and older, the Pediatric

Asthma Quality of Life Questionnaire (PAQLQ(S)) for participants 7 to 11 years of age and a non-asthma specific Pediatric Quality of Life Inventory (PEDSQL) for participants 5 to 6 years of age.

Accounting for Childhood Growth in Cross-Age Studies

'Cross-age' studies that include children need to account for the physical growth and development of study participants. Unlike adult medication dosage, pediatric medication dosage is calculated based on patient weight or body surface area (43), which can change significantly in a relatively short time period. For example, between one and five years of age, children generally double their weight (44). Throughout the course of the study, medication dosage needs to be recalculated and readjusted.

Likewise, the length and height of pediatric patients are also changing, which will affect pulmonary function testing predicted values. Predicted lung function values based on age may be inaccurate if a child has a growth spurt or a growth delay due to chronic disease. A carefully calibrated stadiometer should be used to obtain accurate anthropometric measurements (45, 46).

Physical and Developmental Limitations in Collecting Data

Overall, it is important to measure the clinical variables and study outcomes in a consistent and reproducible manner for all study participants. In 'cross-age' studies, the limitations in the physical capacity and developmental ability of children create a potential challenge. This issue is relevant in the collection of blood, performance of spirometry and sputum induction.

Phlebotomy

Total blood volume is a function of body weight. Variation occurs from institution to institution; however, blood volume limits for phlebotomy are between one and five percent of total blood volume from a single blood draw within a 24 hour period and up to 10% of total blood volume over two months (47). As a result, the phlebotomy limitations in small infants and children demand deliberate consideration in the selection of the most crucial blood tests for a study protocol and may limit the implementation of ancillary or supplementary mechanistic studies.

Spirometry

Although spirometry results are commonly used as outcomes in asthma studies, their use in pediatric, and thus, 'cross-age' studies are more limited, which impacts the choice of study outcomes in cross-age studies. Guidelines for the standardization for adults, school children and pre-school children have been defined (45, 48, 49). The validity of these outcomes is based on participant effort, as well as standardization of procedures. Also, the ability of pediatric participants to provide acceptable spirometry results increases with age. It is estimated that by the age of 5 to 6 years, approximately half can provide acceptable results (50, 51). By the age of 9 to 10 years, 85% to 95% of children provide acceptable results (50, 52).

Sputum Induction

The presence of airway inflammation can be assessed by induced sputum analysis, which also has the advantage of being non-invasive. Although the procedure is generally safe and well-tolerated in children greater than six years of age (53, 54), one may not always be able to obtain adequate induced sputum samples from pediatric participants. In various clinical trials, the

percentage of children with asthma who were able to produce satisfactory samples has ranged from 61% to 92% (55, 56, 57). Higher success rates of sputum induction in children are associated with age greater than 12 years (58). For this reason, the BARD Study will collect induced sputum only for adolescents and adults.

Contraindications to Methacholine Bronchoprovocation Testing

Methacholine bronchoprovocation is used as a research tool to help confirm airway hyperresponsiveness. Because of the rare potential for sudden decreases in FEV_1, one contraindication is poor baseline lung function, which can be difficult to consistently define, especially in a cross-age study population. For pediatric patients, methacholine bronchoprovocation is usually not performed if FEV_1 is below 70% of predicted (59, 60); however, there is greater experience and tolerance for lower FEV_1 values for adult patients (61). In the BARD protocol, different levels of baseline function were tolerated. Methacholine bronchoprovocation could be conducted in adults if $FEV_1$was $\geq$ 55% of predicted and $\geq$1.0 liter at baseline. For study participants less than 18 years of age, the procedure was considered to be safe for $FEV_1 \geq 70\%$ of predicted.

Consideration of Long-Term Effects

Due to the logistical constraints of any clinical trial, the evaluation of the long-term effects of an intervention, positive or negative, can be challenging (62). Cross-age studies that include behavioral and educational interventions can potentially also have long-term spill-over effects on family management or self-management of other chronic conditions (63).

The implications of these effects are further magnified when including children in 'cross-age' studies. Children are still growing and developing, which places them at unique risk for adverse effects, compared to adult participants in clinical trials. Clinical trial interventions can potentially affect a child's long-term health trajectory, asthma disease progression and future adult outcomes (64, 65). In the BARD Study, due to limited data available on the dose-response relationship between escalating ICS dosing and hypothalamic-pituitary adrenal (HPA) axis function in children and adults, the protocol includes an assessment of potential for systemic effects on HPA axis function. This assessment will include overnight urinary cortisol/creatinine as the measure of systemic exposure in all participants. In addition, study participants 5 to 21 years of age will have linear growth monitored by stadiometry.

Challenges in Reporting Data

Instead of separating the analyses of adolescent participants from adult participants, the BARD protocol combines the analyses of all participants aged 12 years and older. AsthmaNet investigators considered that it would be ideal to compare three age groups—5-11; 12-17, and 18 and older; however, the required sample size for these comparison was not feasible. Two age groups would be used. The decision to consider adolescents as part of the "adult" study group to compare to children ages 5-11 was made in order to be consistent with current clinical practice guidelines as well as most FDA regulatory studies. Utilizing these age cutoffs increases the likelihood that the BARD findings would be more easily incorporated into future clinical practice guidelines.

Conclusions

There are several key features to consider in preparation of a cross-age study. Recruitment and consent/ assent of a cross-age population are more challenging and complicated. These procedures must be tailored to the specific demographic characteristics and consent requirements for each population. In addition, cross-age studies need to accommodate some differences in protocol for each age group without compromising the overall hypotheses being tested. For example, the details of interventions (e.g., medication dose), methods of measuring outcomes (e.g., use of parent-based surveys, limits on phlebotomy), or selection of control interventions (e.g., limitations in the use of placebo) may need to be creatively modified. Finally, if subanalyses will be performed, careful consideration should be paid to how data across ages will be subdivided and reported (e.g., age cut-offs, including adolescents as adults or children) to ensure the greatest impact of study results on clinical practice and guideline recommendations.

There is great interest regarding the natural course of asthma phenotypes. Cross-age studies can provide unique information regarding the differences in the diagnosis, treatment and management of asthma in infants, children, adolescents, adults and the elderly. However, substantial challenges are created when participants are recruited across a wide age spectrum. Recognition of these challenges will help better implement studies that provide asthma management recommendations to broader spectrum of patients.

ENDNOTES

1. Yoon EY, Davis MM, El-Essawi H, Cabana MD. FDA labeling status of pediatric medications. *Clin Pediatr.* 2006; 45: 75-7.

2. Szefler SJ, Chmiel J, Fitzpatrick AM, Giacoia G, Green TP, Jackson DJ, Nielsen H, Phipatanakul W. Asthma across the ages: difference between adult and child asthma. *J All Clin Immunol*. [in press].

3. Weiss ST. New approaches to personalized medicine for asthma: Where are we? *J All Clin Immun.* 2012; 129: 327-334.

4. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations; origin, effect and prevention. *J All Clin Immun.* 2011; 128: 1165-1174.

5. Busse WW. Asthma diagnosis and treatment: Filling in the information gaps. *J All Clin Immun*. 2011; 128: 740-750.

6. National Institutes of Health. Request For Applications (RFA) Number: RFA-HL-08-010 Clinical Centers for the NHLBI Asthma Network (AsthmaNet) (U10) http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-010.html. Accessed October 12, 2013.

7. Sutherland ER, Busse WW. Designing clinical trials to address the needs of childhood and adult asthma in NHLBI AsthmaNet. *J Allergy Clin Immunol* [in press]. 2014.

8. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma--United States, 1980-1999. *MMWR Surveill Summ.* 2002; 51: 1-13.

9. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the United States, 1980-2007. *Peds.* 2009; 123: s131-45.

10. Bailey W, Castro M, Matz J, White M, Dransfield M, Yancey, Ortega H. Asthma exacerbations in African Americans treated for 1 year with combination fluticasone propionate and salmeterol or fluticasone propionate alone. *Curr Med Res Opin.* 2008; 24: 1669-82.

11. Brown RW, O'Brien CD, Martin UJ, Uryniak T, Lampl KL. Long-term safety and asthma control measures with a budesonide/formoterol pressurized metered-dose inhaler in African American asthmatic patients: A randomized controlled trial. *J All Clin Immunol.* 2012;130:362-367.

12. Cooper M. Census Officials, Citing Increasing Diversity, Say U.S. Will Be a 'Plurality Nation'. *New York Times.* December 12, 2012.

13. Flores G, Fuentes-Afflick E, Barbot O, et al. The health of Latino children: urgent priorities, unanswered questions, and a research agenda. *JAMA*. 2002;288(1):82-90

14. Yancey AK, Ortega AN, Kumanyika SK. Effective recruitment and retention of minority research participants. *Annu Rev Pub Health*. 2006; 27: 1-28.

15. Fritz GK, McQuaid EL, Kopel SJ, et al. Ethnic differences in perception of lung function: a factor in pediatric asthma disparities? *Am J Respir Crit Care Med.* 2010; 182; 1208.

16. Baptist AP, Thompson M, Grossman KS, Mohammed L, Sy A. Sanders GM. Social media, text messaging, and email-preferences of asthma patients between 12 and 40 years old. *J Asthma.* 2011; 48: 824-830.

17. Sorkness CA, Ford JG, Lemanske RF. Recruitment Strategies in the Asthma Clinical Research Network. *Cont Clin Trials.* 2001; 22: s222-235.

18. Janson C, Wist M. An Internet survey of asthma treatment. *J Asthma.* 2004; 41: 49-55.

19. O'Connor A, Jackson L, Goldsmith L, Skirton H. Can I get a retweet please? Health research recruitment and the Twittersphere. *J Adv Nurs.* 2013. [in press]

20. Title 45, Code of Federal Regulations (CFR)-Part 46, Section 46.116 and 46.117.

21. American Academy of Pediatrics, Committee on Bioethics. Informed consent, parental permission, and assent in pediatric practice. *Peds*. 1995; 34: 314-317.

22. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma *Respiratory Medicine.* 2006; 100, 1307–1317.

23. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med.* 2012; 367: 904-912.

24. Szefler SJ, Eigen H. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. *J Allergy Clin Immunol* 2002;109:730–42.

25. Martin RJ, Szefler SJ, Chinchilli VM, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165:1377–83.

26. Busse WW, Lemanske RF. The placebo effect in asthma: far more complex than simply "I shall please." *J All Clin Immunol*. 2009; 124: 445-6.

27. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. *Designing Clinical Research,* 4th Edition. Lippincott, Williams and Wilkins. Philadelphia, PA 2013.

28. Coffey MJ, Wilfond B, Ross LF. Ethical assessment of clinical asthma trials including children subjects. *Peds.* 2004; 113: 87-94.

29. World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/30publications/10policies/b3/. Accessed October 12, 2013.

30. Miller FG, Shorr AF. Unnecessary use of placebo controls: the case of asthma clinical trials. *Arch Intern Med.* 2002; 162; 1673-7.

31. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Peds.* 2008; 122: 1142-52.

32. Holick MF. Vitamin D: Importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr. 2*004;79:362–371.

33. National Heart, Lung, and Blood Institute. *Expert Panel Report 3: guidelines for the diagnosis and management of asthma—Full report 2007*. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed October 12, 2013

34. Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane TV. Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 questions'. *Prim Care Respir* J. 2009; 18: 83-88.

35. Wood PR, Smith B, O'Donnell L, et al. Quantifying asthma symptoms in adults: the Lara Asthma Symptom Scale. *J All Clin Immunol.* 2007; 120: 1368-72.

36. Cloutier MM, Schatz M, Castro M. et al. Asthma outcomes: composite scores of asthma control. *J All Clin Immunol.* 2012; 129: s24-33.

37. Riley AW. Evidence that school-age children can self-report on their health. *Ambul Pediatr.* 2004;4:s371-6.

38. Olson LM, Radecki L, Frintner MP, Weiss KB, Korfmacher J, Siegel RM. At what age can children report dependably on their asthma health status? *Peds.* 2007; 119: e93-102.

39. Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: exacerbations. *J All Clin Immunol.* 2012; 129: s34-48.

40. Krishnan JA, et al., Asthma outcomes: Symptoms. *J All Clin Immunol.* 2012;129:s124-135

41. Wilson SR, Rand CS, Cabana MD, et al. Asthma outcomes: quality of life. *J All Clin Immunol.* 2012; 129: s88-123.

42. Drotar D. Measuring child health: scientific questions, challenges, and recommendations. *Ambul Pediatr*. 2004;4:353-7.

43. Lack JA, Stuart-Taylor ME. Calculation of drug dosage and body surface area in children. *Br J Anesth.* 1997; 78: 601-605.

44. Centers for Disease Control and Prevention, National Center for Health Statistics. Growth Charts. 2001. http://www.cdc.gov/growthcharts/clinical_charts.htm#Set1. Accessed October 12, 2013

45. Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med.* 2007. 175: 1304-45.

46. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J.* 2005; 26: 153–161.

47. Howie SRC. Blood sample volumes in child health research: review of safe limits. *Bulletin of the World Health Organization*. 2011; 89: 46-53.

48. Miller MR, Hankinson J, Brusasco V, et al. Standardization of spirometry. *Eur Respir J* 2005;26:319–338.

49. Desmond KJ, Allen PD, Demizio DL, Kovesi T, Coates AL. Redefining end of test criteria for pulmonary function testing in children. *Am J Respir Crit Care Med.* 1997;156:542–545.

50. Loeb JS, Blower WC, Feldstein JF, Koch BA, Munlin AL, Hardie WD. Acceptability and repeatability of spirometry in children using updated ATS/ERS criteria. *Pediatr Pulmonol*. 2008; 43: 1020-4.

51. Gaffin JM, Scotola NL, Martin TR, Phipatanakul W. Clinically Useful Spirometry in Preschool-Aged Children: Evaluation of the 2007 American Thoracic Society Guidelines. *J Asthma.* 2010; 47: 762-767.

52. Enright PL, Linn WS, Avol EL, Margolis HG, Hong H, Peters JM. Quality of spirometry test performance in children and adolescents : experience in a large field study. *Chest.* 2000; 118: 665-71.

53. Covar RA, Spahn JD, Martin RJ, et al. Safety and application of induced sputum analysis in childhood asthma. *J Allergy Clin Immunol.* 2004; 114: 575-582.

54. Gibson PG, Grootendorst DC, Henry RL, Pin I, Rytila PH, Wark P, Wilson N, Djukanovic R. Sputum induction in children. *Eur Respir J.* 2002; 20: 44s–46s.

55. Wilson N, Bridge P, Spanevello A, Silverman M. Induced sputum in children: feasibility, repeatability, and relation of findings to asthma severity. *Thorax.* 2000; 55: 768-774.

56. Jones PD, Hankin R, Simpson J, Gibson PG, Henry RL. The Tolerability, Safety, and Success of Sputum Induction and Combined Hypertonic Saline Challenge in Children. *Am J Respir Crit Care Med.* 2001; 164: 1146–1149.

57. Li AM, Tsang TW, Chan DF, Lam HS, So HK, Sung RY, Fok TF. Sputum induction in children with asthma: a tertiary-center experience. *Pediatr Pulmonol.* 2006; 41: 720-5.

58. Lex C, Payne DN, Zacharasiewicz A, Li AM, Wilson NM, Hansel TT, Bush A. Sputum induction in children with difficult asthma: safety, feasibility, and inflammatory cell pattern. *Pediatr Pulmonol.* 2005; 39:318-24.

59. Covar RA, Colvin R, Shapiro G, Strunk R. Safety of methacholine challenges in a multicenter pediatric asthma study. *J Allergy Clin Immunol.* 2006;117:709-711.

60. Childhood Asthma Management Program Research Group. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. *Control Clin Trials.* 1999;20:91-120.

61. Martin RJ, Wanger JS, Irvin CG, Bucher Bartelson B, Cherniack RM. Methacholine challenge testing: 731 safety of low starting FEV1. Asthma Clinical Research Network (ACRN). *Chest.* 1997;112:53-6.

62. Hausner E, Fiszman ML, Hanig J, Harlow P, Zornberg G, Sobel S. Long-term consequences of drugs on the paediatric cardiovascular system. *Drug Saf.* 2008; 31: 1083-96.

63. Clark NM, Mitchell HE, Rand CS. Effectiveness of educational and behavioral asthma interventions. *Peds.* 2009; 123: s185-92.

64. Quizon A, Colin AA. Special considerations in pediatric asthma. *Curr Opin Pharmacol*. 2010; 10: 272-5.

65. Szefler SJ. Advances in pediatric asthma in 2012: moving toward asthma prevention. *J All Clin Immunol.* 2013; 131: 36-46.

66. American Academy of Pediatrics, Committee on Drugs and Committee on Pediatric Research. Clinical Report: Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Peds.* 2010; 125:850-860.

Table 1: Challenges with Studies Evaluating Cross-Age Response to Asthma Treatment

Issue	Example(s)
Recruitment	- Need for culturally diverse recruitment materials - Need for Age-appropriate recruitment strategies
Consent/Assent	- Requirement of parental/guardian consent for minors - Incorporation of Assent procedures for children
Intervention Selection	- Difficulty in maintaining consistency of intervention therapy due to differences in dosing and drug availability
Control Selection	- Limitations in the use of placebo controls for children
Outcome Measurement	- Dependence on proxy reporting of outcomes for children - Dearth of cross-age instruments to measure quality of life, asthma control, symptoms and exacerbations
Participant Growth & Development	- Need to account for physical growth (e.g., weight, height) of pediatric participants
Physical Limitations in Data Collection	- Physical and developmental limits for testing and data collection (e.g., phlebotomy, spirometry, sputum induction) - Increased safety restrictions in testing of children (e.g., methacholine bronchoprovocation)
Consideration of Long-term Effects	- Careful monitoring and follow-up for long term developmental effects in children
Reporting of Results	- Determination of how data across ages will be subdivided (e.g., age cut-offs, including adolescents as adults or children)

Table 2: BARD Study ICS Dosing in Children aged 5-11 and Adults/Adolescents aged ≥12Years

	Children		Adolescents/Adults	
Run In Dose	1 x ICS	50 mcg fluticasone propionate BID	1 x ICS	100 mcg fluticasone propionate BID
Phase A	2 x ICS	100 mcg fluticasone propionate BID	2.5 x ICS	250 mcg fluticasone propionate BID
Phase B	5 x ICS	250 mcg fluticasone propionate BID	5 x ICS	500 mcg fluticasone propionate BID
Phase C	2 x ICS + LABA	100 mcg fluticasone propionate & 50 mcg salmeterol BID	1 x ICS + LABA	100 mcg fluticasone propionate & 50 mcg salmeterol BID
Phase D	5 x ICS + LABA	250 mcg fluticasone propionate & 50 mcg salmeterol BID	2.5 x ICS + LABA	250 mcg fluticasone propionate & 50 mcg salmeterol BID

Table 3: Conditions Under Which Placebos May be Ethically Used in Pediatric Drug Research*

1. When there is no commonly accepted therapy for the condition and the agent under study is the first one that may modify the course of the disease process
2. When the commonly used therapy for the condition is of questionable efficacy
3. When the commonly used therapy for the condition carries with it a high frequency of undesirable adverse effects and the risks may be significantly greater than the benefits
4. When the placebo is used to identify incidence and severity of adverse effects produced by adding a new treatment to an established regimen
5. When the disease process is characterized by frequent, spontaneous exacerbations and remissions and the efficacy of the therapy has not been demonstrated.

* *Modified from the American Academy of Pediatrics, 2010 (66)*