Environmental Control as Add-on Therapy in Childhood Asthma

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JHM IRB - eForm A – Protocol

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1. Abstract

High indoor allergen and pollutant levels have repeatedly been linked to asthma morbidity, especially among urban children, who have among the highest asthma morbidity in the US. [1-5] However, environmental intervention trials for asthma have typically compared an environmental control strategy (ECS) to no intervention, a design that does not reflect the recommended approach to asthma management, which includes ECSs *in conjunction with* titration of controller medication. [6] As a result, it remains unknown whether the addition of an ECS to controller medication titration results in improved asthma control, and therefore a reduced controller medication requirement. Another unanswered question is whether the addition of an ECS to controller medication titration results in greater reduction of allergic inflammation than medication titration alone. ECSs may have a greater effect on allergic inflammation than controller medications because ECSs target the most upstream point of the asthma inflammatory pathway by reducing pro-inflammatory environmental exposures, while controller medications target a downstream point of this pathway. [7-9] Surprisingly, it is also unknown whether the improvement in asthma in ECS trials is mediated by reductions in allergen levels and/or reduction in pollutant levels. Understanding the factors that mediate the effects of an ECS on asthma is important for refuting, or supporting, a causal role for indoor allergens and/or pollutants in asthma morbidity, and also for optimizing the design of ECSs to target the most influential factors. We therefore hypothesize that the addition of an individually-tailored, multi-faceted ECS to guidelines-based controller medication titration will result in less controller medication requirement and allergic inflammation than controller medication titration alone among urban asthmatic children. We will test this hypothesis and identify the factors that mediate the clinical effects of the ECS with a parallel-arm, randomized controlled trial of ECS plus controller medication titration vs. controller medication titration alone. Our aims are: **(1)** To determine the effect of the addition of ECS to controller medication titration on controller medication requirements and allergic inflammatory biomarkers, and (2) To determine whether reductions in particulate matter (PM) and/or indoor allergens mediate the effects of an ECS on asthma. This proposed trial will answer a pivotal question because if ECSs do not provide additional benefit in the context of treatment with controller medication, the role of ECS in asthma management should be downgraded. On the other hand, if ECSs do indeed reduce controller medication requirements, greater emphasis should be placed on the importance of ECSs in asthma management, studies should be conducted to identify best ECS practices, and policies should be changed to require third party payers to cover ECS costs.

2. Objectives

We hypothesize that the addition of an individually-tailored, multi-faceted environmental control strategy (ECS) to guidelines-based controller medication titration will result in less controller medication requirement and allergic inflammation than controller medication titration alone among urban asthmatic children. We will test this hypothesis and identify the factors that mediate the clinical effects of the ECS with a parallel-arm, randomized controlled trial of ECS plus controller medication titration vs. controller medication titration alone. The aims are:

(1) To determine the effect of the addition of ECS to controller medication titration on controller medication requirements and allergic inflammatory biomarkers.

   a) To compare the effect of the active intervention ("ECS+Medication Group") to control ("Medication Group") on controller medication requirement ("treatment step") and inhaled corticosteroid dose.
   b) To compare the effect of the active intervention to control on F_ENO, serum allergen-specific IgE levels.

(2) To determine whether reductions in particulate matter (PM) and/or indoor allergens mediate the effects of an ECS on asthma.

   a) To measure the change in fine and coarse particulate matter ($PM_{2.5}$ and $PM_{2.5-10}$, respectively) and indoor allergen concentrations (cat, dog, mouse, cockroach, and dust mite) among study participants.
   b) To estimate the causal effects of PM and allergen exposure reduction on controller medication requirements and allergic inflammatory outcomes, using a novel statistical approach, principal stratification analysis.

(3) To evaluate whether a child's personal bacterial exposures, particularly those of animal origin, contribute to asthma morbidity.
   a) To compare bacterial community profiles and *S. aureus* genotypes in children versus pet and pest animals (dog, cat, mouse, cockroach others) in the home.
   b) To examine associations between the child's bacterial communities and asthma morbidity.
   c) To determine relationships between the child's *S. aureus* colonization and asthma morbidity.

3. Background

Despite the marked reduction in asthma morbidity across the US as a whole since the widespread use of inhaled corticosteroids,[10, 11] there has been little to no effect on asthma morbidity among urban children with asthma. Although this disproportionate burden of asthma morbidity has many causes, one major cause is thought to be the high levels of certain indoor allergens and pollutants found in homes in urban communities.[2] Although we know that an individually-tailored, multi-faceted ECS that targets these allergens and pollutants is effective in reducing asthma symptoms and exacerbations in urban children,[12-14] this type of intervention is rarely a component of the clinical care of urban children. There are several reasons why ECSs have not moved from the research to the clinical care arena.[15] For health care providers, there are fewer barriers to writing prescriptions for medications than to counseling patients about ECS; and for patients, there are fewer barriers to taking medications than to implementing an ECS. These barriers include little reimbursement of health care providers for ECS counseling and lack of coverage for ECS durable goods and services. Until there is clinical trial data that directly demonstrates that the addition of an ECS to controller medication titration results in meaningful reduction of controller medication needs, it will be very difficult, if not impossible, to make the compelling argument that is needed in order to remove these barriers. This type of clinical trial data would also allow direct comparisons of the cost of the ECS intervention to the cost of the controller medication that would have been needed without the addition of the ECS. When framed in terms of medication equivalency (for both effectiveness and cost), a much more compelling argument can be made to require third party payers to cover ECS services, and to place greater emphasis on ECS in practice guidelines. However, even if an ECS provides little controller medication sparing effect, this will be a critically important result because it would provide a strong evidence base for placing greater emphasis on, and allocating resources towards, improving implementation of controller-medication titration protocols.

Environmental Control Strategy: As the next logical step following a large body of work linking indoor allergen and pollutant exposure to asthma morbidity in urban children, members of the investigator team have led several ECS trials focusing on both indoor pollutant and allergen reduction. The pollutants and allergens targeted in our studies are all present in high concentrations in Baltimore homes and have all been repeatedly implicated in asthma morbidity in this population.

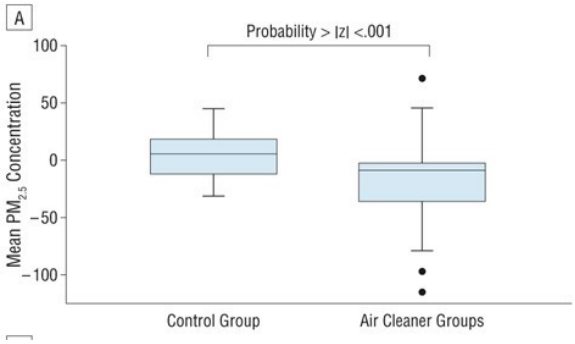


Figure 1. Boxplots reflect the change in $PM_{2.5}$ in the control and air cleaner groups, respectively.

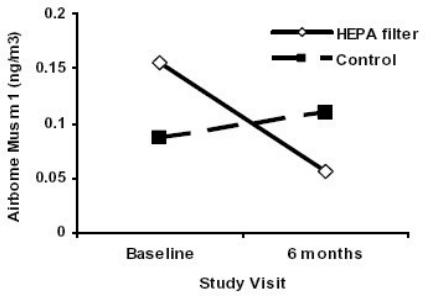
PARTICULATE MATTER

The Particulate Reduction Education in City Homes (PREACH) trial was an RCT in 126 Baltimore asthmatic children living with a smoker.[14] Participants were randomized to one of three arms: high efficiency particulate air (HEPA) purifiers, HEPA purifiers plus a behavioral intervention, or delayed air purifiers (control group). Participants were followed for six months. Participants who received air purifiers had ~50% reduction in both $PM_{2.5}$ and $PM_{2.5-10}$ concentrations (Figure 1) and an increase in symptom-free days of 1.9 days/2 week period compared to the control group. In a second intervention study, twenty-six adult former smokers with COPD had placement of two HEPA purifiers in their non-smoking homes and $PM_{2.5}$ and $PM_{2.5-10}$ measured before and after air purifier placement. Both $PM_{2.5}$ and $PM_{2.5-10}$ concentrations were reduced by ≥60%, demonstrating that even in nonsmoking homes, air purifiers alone result in a substantial reduction in PM.[16]

INDOOR ALLERGENS

(1) Pest Allergen Reduction: The Mouse Allergen and Asthma Intervention Trial (MAAIT) is a multi-center RCT of a mouse allergen exposure intervention (U01AI083238). Currently, ~300 of 350 mouse sensitized children and adolescents have been randomized to either the Integrated Pest Management (IPM) or the Education arm and retention is ~90%. Because the trial is still underway, we do not yet know the effect of the intervention on mouse allergen levels or clinical outcomes. However, participants are repeatedly assessed for persistent or recurrent mouse infestation to determine if they will receive additional professional pest management, so we do know that >60% of participants in the IPM arm have had complete eradication of their infestation. As a result, we expect that the IPM arm will also have a marked reduction in mouse allergen levels in their homes. Indeed, a pilot study using a similar IPM protocol observed a 75% reduction in home mouse allergen levels by five months post intervention. Several other trials with a focus on cockroach allergen, including one in Baltimore, have also demonstrated substantial reductions in cockroach allergen with an IPM intervention. These studies provide strong preliminary data to support the efficacy of IPM interventions in reducing home pest allergen levels.

Figure 2. Room air filters and airborne Mus m 1 concentrations. 65 homes were randomized to receive bedroom air HEPA filters or no intervention. Airborne Mus m 1 was quantified at baseline and 6 months. Mus m 1 concentrations are depicted on the y-axis and expressed in ng/m^3. Intervention (solid line, hollow diamonds), n=34; Control (dashed line, solid squares), n=31; p = 0.26.



(2) Airborne Allergen Reduction with Air Purifiers: Furry animal allergens are readily detected in air samples because they are found on small particles, typically those ≤10microns. Air filtration is effective not only in reducing indoor PM, but also furry animal allergens, so will be included as a component of our ECS intervention. For example, a Baltimore-based environmental intervention study indicates that room air purifiers reduce airborne mouse allergen levels. In this study, 65 asthmatic children were randomized to receive either a bedroom filter or no intervention. At six months, airborne mouse allergen levels had decreased by 68% in the intervention group, but had increased in the control group. This marked degree of reduction was achieved even though there was no IPM intervention targeting

mouse infestation in this study. (Figure 2) Other studies have also demonstrated reductions in other airborne animal allergens, including cat and dog.[17, 18]

(3) Microbial exposures: While bacterial exposures are known to influence the development of asthma, less is known about their impact on symptoms and lung function among children diagnosed with asthma. Further, it is not known whether the profile of bacterial exposures (*e.g.* in the nasal microbiome) or exposure to a single bacterium is important. A leading candidate bacterium is the Gram-positive *Staphylococcus aureus,* which colonizes a third of the U.S. population. *S. aureus* is known to exacerbate atopic eczema through its pro-inflammatory activity, primarily via a Th2, or allergic, immune response to bacterial superantigen proteins such as staphylococcal enterotoxins (SE). Emerging data indicate that *S. aureus* exacerbates upper respiratory disease via the same pathway, and there is evidence for a causal role of *S. aureus* in the development of chronic rhinosinusitis with nasal polyposis.[19] A number of limited but provocative studies suggest that *S. aureus* may also exacerbate asthma;[20, 21] and our study using NHANES data demonstrates that *S. aureus* colonization is an independent risk factor for current asthma and emergency department (ED) visits for asthma among children and young adults. Our pilot work demonstrates that the presence of pet and pest animals in the household contribute to bacterial exposures and may modify risk for colonization with *S. aureus*. Presence of pest mice in urban households was associated with a two-fold increased likelihood of environmental *S. aureus* contamination. In a controlled trial of people with *S. aureus* infection, we identified both pet carriage and presence of pests in the home as risk factors for human *S. aureus* colonization, and we found that pets generally enhanced bacterial sharing among household members.

This combined experience in ECS trials demonstrates that air purifiers reduce airborne $PM_{2.5}$ and $PM_{2.5-10}$ in homes with and without smokers, and mouse allergen. In addition, our IPM intervention eradicates mouse infestation in most homes. Others have also found that IPM reduces cockroach and mouse allergens and air purifiers reduce other furry animal allergens, including cat and dog.[22-24] Because we are combining strategies that have proven successful for individual pollutants or allergens, we expect that the proposed ECS will be more effective at reducing proinflammatory environmental exposures than any of the single exposure interventions, and will therefore have greater effects on asthma control, resulting in reduced medication needs.

3. Study Procedures a. Study design, including the sequence and timing of study procedures

Overview: The study is a parallel arm, randomized, controlled trial (RCT) of an individually tailored, multi-faceted ECS plus controller medication titration versus controller medication titration alone. After an approximate 4-week run-in period to stabilize their asthma, we will randomize 200 Baltimore 5-17 year olds with persistent asthma and a recent exacerbation in a 1:1 ratio to the two arms and follow them for six months. Participants will have repeated assessment of: controller medication requirements; secondary clinical, physiologic, and inflammatory outcomes; and PM, air nicotine, and allergen levels.

Table 1. Study Visits

	Screening CV	HV-1	CV-1	INT 1	CV-2	INT 2**	HV-2	INT 3	CV-3	INT 4	CV-4	HV-3
Months	-1.5	-1.5-0	0		2		3		4		6	6
Windows			~ + 2 wks		+/- 2 wks		+/-2 wks		+/- 2 wks		+/- 2 wks	+/- 2 wks
Consent Process	X											
Allergy Skin Testing	X											
Physical Exam	X		X		X				X		X	
Venipuncture	X										X	
Urine collection	X		X		X				X		X	
Buccal swabs			X		X				X		X	

Microbial swabs			X		X				X		X	
Nasal Mucus Sample			X		X				X		X	
Questionnaires	X		X		X				X		X	
Spirometry	X		X		X				X		X	
FeNO	X		X		X				X		X	
Adherence Assessment			X		X				X		X	
Medication adjustment	X		X		X				X		X	
Randomization			X									
Home assessment		X					X					X
Settled dust collection		X					X					X
Air sampling including $PM_{2.5}$ & PM_{10}		X					X					X
Air nicotine sample collection		X										X
Surface swabs		X					X					X
Bacterial Questionnaire		X					X					x
Pet sampling/Questionnaire (if pet present)		X					X					X
SES Questionnaire		X										
Intervention Module				X		X**		X		X		
**Only participants sensitive to mouse or cockroach will receive INT 2.												

Screening Visit

Skin testing: Allergy skin testing will be performed to 14 allergens, using the MultiTest device (Lincoln Diagnostics, Decatur, IL). The allergen extracts to be used are: dog, cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, rat epithelia, German cockroach, American cockroach, mouse epithelia, tree pollen mix, grass mix, *Alternaria*, *Aspergillus*, common ragweed, and *Cladosporium*. A positive skin test will be defined as a net wheal ≥2mm. Skin test results performed by the study team within the last year may be used for inclusion criteria. We define the mean wheal diameter as the average of the largest diameter and the corresponding midpoint diameter. Participants who are not able to have skin testing done at the screening visit or who are skin test negative may have blood drawn for specific IgE test to dog, cat, rat, Dermatophagoides farinae along with mouse and cockroach.

FENO and Lung Function: FENO is a known marker of pulmonary inflammation and will provide a non-invasive means of assessing pulmonary inflammation in a large cohort that includes children. Measurement of exhaled nitric oxide will be obtained prior to lung function according to the American Thoracic Society Guidelines[25] using a handheld, FDA-approved analyzer (NIOX TM System, Aerocrine, Sweden). Pre- and post-bronchodilator lung function testing will be performed according to ATS guidelines.[26] After the pre-bronchodilator lung function testing is done, the participant will be given one unit dose of nebulized albuterol (2.5mg and spirometry will be repeated approximately 15-20 minutes following administration of albuterol. Bronchodilator reversibility will be defined as a ≥12% increase in FEV1 after short-acting bronchodilator.

Venipuncture: A venous blood sample will be obtained so that the serum can be used to measure mouse, cockroach, staphylococcal enterotoxin-specific IgE levels in the Matsui laboratory using the ImmunoCAP system (ThermoFisher, Uppsala, Sweden). Participants who are not able to complete prick puncture skin testing, or have a negative skin test but strong clinical evidence, will have specific IgE test to dog, cat, Dermatophagoides farinae, and rat along with mouse and cockroach.

Questionnaires: Questionnaires that capture medication use, asthma symptoms, asthma-related health care utilization will be administered at all clinic visits. The questionnaires are based on questionnaires used in urban populations and

will capture symptoms over a two week period of time, and medication use over a two week period of time as well as asthma control as assessed by the validated Asthma Control Test.[27, 28] Asthma severity will be assessed by the validated Composite Asthma Severity Index (CASI).[29] Asthma control will be assessed at CV1-4 slightly different from the screening visit. (See assessment Tables 2 and 2a).

Table 2. Assessment of Control Level at CV0

	Days of asthma symptoms or rescue medication use/previous 2 weeks	Nights of wakening with asthma symptoms or for rescue medication use/previous 2 weeks	FEV_1 percent predicted	Steroid bursts, previous six months
Control Level 1	**0-3**	**0-1**	**≥85%**	**0**
Control Level 2	**4-9**	**2**	**80-<85**	**1**
Control Level 3	**10-13**	**3-4**	**70-<80**	**2**
Control Level 4	**>13**	**5-14**	**<70**	**>2**

Table 2a. Assessment of Control Level at CV1-4

	Days of asthma symptoms or rescue medication use/previous 2 weeks	Nights of wakening with asthma symptoms or for rescue medication use/previous 2 weeks	FEV_1 percent of best (the best FEV1 they've had since starting the study)	Steroid bursts, since last visit
Control Level 1	**0-3**	**0-1**	**>85%**	**NO**
Control Level 2	**4-9**	**2**	**80-<85**	**YES**
Control Level 3	**10-13**	**3-4**	**70-<80**	**-**
Control Level 4	**>13**	**5-14**	**<70**	**-**

Because school age children and adolescents will be enrolled, we will administer the questionnaires to the primary caregiver of children 5-11 years, and to both the study participant and his/her caregiver for adolescent study participants, age 12-17. The questionnaires will be modified accordingly. Although previous studies have indicated concordance between the adolescent's and the caregiver's responses,[30] we will collect data from both so that we have the ability to assess the concordance rate within our study population.

Urine collection: Urine will be collected for pregnancy testing in females of childbearing capacity. Urinary cotinine will be assessed by a rapid detection method to exclude active smokers in children 12 and older. In children 12 and older, a NicAlert value of 4 or greater will exclude them from eligibility for randomization. Urine will also be stored for later analysis of cotinine in all children to assess second hand smoke exposure.

Buccal swabs for RNA, DNA extraction: The inside cheek will be swabbed to collect RNA and DNA. Approximately 7 swabs will be collected. Samples will be analyzed to determine if the environmental intervention is associated with epigenetic changes in candidate allergy-, asthma-, inflammation- or immune-related genes (DNA methylation and related RNA expression).

Physical Exam: A brief physical exam will be performed by the study physician. Height, weight, and waist measurements may be performed by study team. At follow-up clinic visits a focused exam will be performed.

Adherence Assessment: Participants will be required to bring their medications to all study visits and provided a small monetary incentive to do so (see below under Payment and Remuneration). Medications that will be used (see treatment algorithm below) will include dose counters. At the screening visit, since participants will be on a range of treatment regimens, many of which will not include dose counters, adherence will be assessed by questionnaire. At all other visits, adherence will be assessed both by questionnaire and the dose counter. Participants with <25% adherence at CV1 will not be eligible to be randomized.

Table 3. Treatment Steps	
Step 0	**albuterol prn**
Step 1	**fluticasone 50mcg QD**
Step 2	**fluticasone 50 mcg BID**
Step 3	**fluticasone 100mcg BID**
Step 4	**fluticasone 250mcg BID**
Step 5	**fluticasone/salmeterol 250/50 BID**
Step 6	**futicasone/salmeterol 500/50 BID**

Treatment Algorithm: The treatment algorithm is based on national asthma treatment guidelines and adapted from algorithms that have been successfully implemented by the NIH-funded Inner-city Asthma Consortium and Rho Federal Systems Division, Inc.[32, 33] At each clinic visit, the participant's control status will be assessed using recent symptom history, exacerbation history, and lung function. The participant's treatment will be prescribed based on a combination of his/her current treatment step, control level, and adherence. This algorithm-driven medication titration approach has been used successfully in other inner-city asthma studies. Participants who meet eligibility criteria at the screening clinic visit will have the treatment algorithm applied and will be sent home after education about asthma and their prescribed medication and dispensing of the prescribed medication by the pharmacy. (Note: the pharmacy or study staff may deliver medication to the participant's home). On call coverage will be provided for participants. If participants have a primary care provider, a letter will be sent notifying the provider that we will be taking over the participant's asthma care while in the study. Participants who are not eligible will be referred back to their asthma care providers for continued asthma management.

Table 4. Treatment Algorithm CV0

Current Regimen	Current Control Level	Treatment Assigned
No Controller	1	Step 0
	2	Step 2
	3	Step 2
	4	Step 3*
Step 1	1	Step 1
	2	Step 2
	3	Step 2
	4	Step 3*
Step 2	1	Step 2
	2	Step 3
	3	Step 3
	4	Step 4*
Step 3	1	Step 3
	2	Step 4
	3	Step 4
	4	Step 5*
Step 4	1	Step 4
	2	Step 5
	3	Step 5
	4	Step 6*
Step 5	1	Step 5
	2	Step 6
	3	Step 6
	4	Step 6*
Step 6	1	Step 6
	2	Step 6
	3	Step 6*
	4	Step 6*

*may also require prednisone burst

Control Assessment (Tables 2 and 2a): The participant's level of control will be assessed according to the rubric depicted in Tables 2 and 2a.

Assessment of Current Treatment Step (Table 3): At the screening visit, the participants will be assigned a current treatment step based on their current medication regimen and level of adherence to this regimen. Although almost 100% of participants' insurance is expected to cover the drugs in Table 3, for the participants whose insurance will not cover the drugs listed in Table 3, alternative comparable regimens that are appropriate are listed below.

Treatment Assignment (Tables 4 and 4a): The treatment step that will be assigned will be based on the participant's current control level, current treatment step, lung function, and adherence. The study doctor may override the algorithm when it is in the best interest of a participant's care. The participant's asthma will be managed by the study physicians for the duration of the study and the participant's parent/guardian will be provided a 24 hour pager number to access study physicians for concerns related to their child's asthma.

Table 4a. Treatment Algorithm CV1-CV4

For CVs 1-4, adherence is taken into account for the treatment assignment as follows: Control level	Treatment Algorithm for Participants with ***Unacceptable Adherence (<50%)***	Treatment Algorithm for Participants with ***Acceptable Adherence (≥50%)***
1	Continue same controller regimen	If on treatment steps 1-6, decrease controller regimen by 1 step. If on step 0, continue step 0.

2	Continue same controller regimen or place on step 2 therapy, whichever is higher.	Increase controller regimen by 1 step, or continue step 6 therapy if already on step 6.
3	Continue same controller regimen or place on step 2 therapy, whichever is higher	**SYSTEMIC STEROID USE=0 (no)** • If on steps 0-5, increase controller regimen by 1 step. • If on step 6, continue step 6 or treat with step 6 and a 4 day burst of prednisone. **SYSTEMIC STEROID USE=1 (yes)** • If on steps 0-4, increase controller regimen by 2 steps. (continued on next page)
3 (continued)		• If on treatment step 5, increase controller regimen to step 6 or treat with step 6 and a 4 day burst of prednisone. • If on treatment step 6, continue step 6 or treat with step 6 and a 4 day burst of prednisone.
4	Continue same controller regimen, or place on step 3 therapy, whichever is higher OR Treat with 4-day prednisone burst and continue same controller regimen or place on step 3 therapy, whichever is higher	• If on steps 0-4, increase controller regimen by 2 steps. • If on step 5, increase to step 6 OR treat with step 6 and a 4 day prednisone burst. • If already on step 6, continue step 6 or treat with step 6 and a 4 day prednisone burst.
Adherence is assessed by the dose counter and calculated as the (number of doses taken/number of doses prescribed)*100. If the participant does not bring his/her controller medications to the visit, the **Medication Adherence Review** will be used to estimate adherence.		

Household Members with Asthma: The parent/guardian will be asked about other members of the household who have asthma. These household members will be identified by number only. Age, sex, and information about asthma related health care utilization will be collected from the participant's guardian about other household members who have asthma. If there are other children with asthma, not including the study participant (index child), we will ask the child, 5-17 years of age, and his/her parent/guardian to participate in a sub study. We will ask to draw one tube of blood for specific IgE to cat, dog, mouse, rat, German cockroach, and D. farinae and ask that the Asthma Control Test questionnaire be completed by the child around the time of randomization and the end of the study. This will require a separate consent form. If there is more than one child 5-17 years of age in the household with the index child, the child who will be asked to participate in the study will be chosen based on convenience. The purpose of this sub study is to generate preliminary data to understand how many other household members have asthma and whether the intervention affects asthma control of other children with asthma in the household.

URI Assessment: The parent/guardian and/or adolescent child will be asked questions about recent respiratory illnesses (colds) and a nasal mucus sample will be collected. The child will use a nasal saline spray in each nostril and blow his/her nose into a plastic baggie for the collection of a nasal sample. This will be collected at CV1-4.

Run-in Period and Follow-up Clinic Visits: There will be an approximate 4 week run-in period following the screening visit to stabilize the participant's asthma. Participants will return for CV1 for randomization if they meet adherence eligibility requirements. Once randomized, participants will be prescribed a steroid burst to have at home in the event of an exacerbation. They will then have follow-up CVs every two months with clinical assessment of their asthma, collection of outcome data, and application of the treatment algorithm as described above (Table 2).

Swabs for microbial assessment: The nares, oropharynx, and skin will be sampled using Copan E-swabs™ (Copan Diagnostics, Murrieta, CA) for staphylococcal culture and Catch-All™ sample collection swabs (Epicentre Biotechnologies, Madison, WI) for bacterial community analysis at CV1,2,3,and 4. The child may self-swab with the help of a parent/guardian.

At HVs: Home Assessment Visits (HV) will occur at baseline, 3 and 6 months. Home inspection, settled dust collection, PM_{10}, $PM_{2.5}$, airborne allergen measurements, and microbial air sampling may occur at all HVs. The air sampling of microbes and their products will be compared to dust samples collected. $PM_{2.5-10}$ will be calculated, as done in previous studies, by subtracting the $PM_{2.5}$ concentration from the PM_{10} concentration that is measured adjacent to, and simultaneously with, the $PM_{2.5}$ measurement. A passive filter for air nicotine monitoring will be placed in the home at baseline and 6 months.

Home inspection: A trained technician will conduct a home inspection to collect data regarding the home environment, including condition of dwelling, evidence of tobacco smoking, evidence of pets and pests.

Dust sample collection: Dust will be collected from the bed and bedroom floor using a standard procedure. The dust samples will be analyzed for the major relevant indoor allergens: Mus m 1, Der f 1, Fel d 1, Can f 1, and Bla g 1. A portion of the bedroom dust sample will be saved for future studies. A separate dust sample will be analyzed for bacterial communities and *S. aureus*, including staphylococcal enterotoxin proteins that may be secreted by the bacterium. Additional dust will be collected from standardized home surface sites using sterilized electrostatic cloths (autoclaved Swiffer™, Proctor & Gamble, Cincinnati, OH) for bacterial culture. Temperature and humidity data may also be collected.

If a participant moves between home visits, and the participant is randomized to receive intervention, an attempt will be made to collect another dust sample prior to the intervention visit.

URI Assessment: A respiratory illness questionnaire will be completed at the 3 month (HV2) home visit.

Socioeconomic Questionnaire: A questionnaire about specific socioeconomic factors will be administered at the first home visit.

Bacterial Questionnaires: At the home visit we may collect data on established risk factors for acquisition of *S. aureus* and other bacteria, such as daycare, gym use, and antibiotic use, and household location (which will be collected on a separate form, then geocoded into X, Y coordinates from address data before linkage with health or demographic data).

Pet Questionnaire: We may collect data on participant contact with and characteristics of pet animals in the home. These data will include notations from visual inspection of the pets and areas of the house related to pets (e.g. pet crates).

Sampling of pets and pests: Under an approved ACUC protocol (Davis, SP14H352, 9/18/2014-9/18/2017), Copan Eswabs™ (Copan Diagnostics, Murrieta, CA) for bacterial culture and Catch-All™ sample collection swabs (Epicentre Biotechnologies, Madison, WI) for bacterial community analysis may be collected from all pet animals at multiple anatomical sites and from freshly trapped rodents and other trapped pests. The informed consent process for these pet swabs will be conducted under the approved ACUC protocol and conducted by the Davis group. Study participants randomized to pest control will be given a magnet with a number to call to schedule optional pick-up of freshly trapped rodents and other pests from the home to transport to the laboratory for bacterial sampling.

Particulate Matter and Airborne Animal Allergens: Particulate matter monitoring will be conducted in the child's bedroom using integrated sampling direct-reading methods for an approximate 5 day period. Air samples for $PM_{2.5}$ and PM_{10} will be collected using methods developed during previous childhood asthma studies.[34] After gravimetric analysis, the PM_{10} filters will be assayed for allergen content in the Matsui laboratory. PM_{10} samples will be analyzed because previous research indicates that the bulk of airborne animal allergens is contained on particles less than 10µm in aerodynamic diameter.[35, 36] Microbial air sample measurements may be obtained.

Inspirotec air monitors will be deployed in a subset of homes to establish correlation between our PM10 measurements of airborne biomass and Inspirotec spectroscopic measurements of biomass. We will also compare the limits of detection of the two methods and validate the utility of the Inspirotec sampler as easily deployable in home environments.

Randomization: Participants will be randomized within 6 weeks (+/- 2 wks) of the screening clinic visit in a 1:1 ratio using a statistical software package to generate random numbers. The randomization scheme will be developed by the Data Management and Analysis Core (DMAC). Participants will be randomized in random block sizes of 4 to 8. The randomization scheme will be embedded into the recruitment/tracking database so that once a participant meets all eligibility criteria the site study coordinator can activate randomization through a secure user interface. The DMAC database programmer will have access to the computer code for the randomization scheme. Participants randomized to the ECS+Medication Group will be scheduled for an intervention prior to their next clinic visit.

ECS Intervention

Skin test data, home inspection data, and environmental history will be used to tailor an ECS to participants randomized to the ECS+Medication Group. Randomization will occur at CV1 and all of the information needed to assign ECS modules will have been collected before randomization. The 5 modules are listed below along with the qualifying criteria to receive the module and a summary of the components of each module (Table 5).

Table 5. Individually-Tailored, Multi-Faceted Environmental Control Strategy Intervention

	Qualifying criteria	**Components of Module**
Rodent module	Positive skin test or IgE* to mouse or rat plus any evidence of infestation on home inspection OR parent report of evidence of infestation in the past month	Professional IPM Targeted cleaning IPM education Allergen-proof mattress and pillow encasements
Cockroach module	Positive skin test or IgE* to cockroach plus any evidence of infestation on home inspection OR parent report of evidence of infestation in the past month	Professional IPM Targeted cleaning IPM education Allergen-proof mattress and pillow encasements
Furry pet module	Positive skin test or IgE* to cat or dog	Education Allergen-proof mattress and pillow encasements Targeted cleaning
Dust mite module	Positive skin test or IgE* to dust mite	Education Allergen-proof mattress and pillow encasements Targeted cleaning
SHS module	Smoker in the home	Education
Air purifiers/Clean Bedding	None – everyone assigned to the ECS+medication arm will receive air purifiers and child's bedding will be replaced with study bedding for study duration.	Deployment of 2 portable air purifiers, one in the child's bedroom and one in the TV/living room. Child's bedding will be replaced with study bedding for study duration.

*≥2mm net wheal or specific IgE ≥ 0.35

Professional IPM will be delivered by a local pest management company using protocols we have developed for other studies. For rodents, the intervention will include placement of traps, application of rodenticide in cracks and sealing of cracks and holes that can serve as an entry point for rodents. For cockroaches, the intervention will be based on previous successful protocols[22, 24] and will include placement of Advion (indoxacarb), a low-toxicity gel bait, and sticky traps for monitoring of cockroach infestation. Indoxacarb is the active ingredient in pesticides used on pomme fruits such as apples and in products used to kill fleas on cats and dogs. It is a commercially available pesticide for cockroach control and will be applied by licensed exterminators according to the manufacturer's instructions.

Parents/guardians will be asked to place the sticky traps 3-4 days prior to the IPM visit so that the location(s) of cockroach activity can be accurately identified. They will be given detailed instructions along with the sticky traps. The study team may assign a team member to place the traps for the family if this seems necessary. If for some reason, traps are not placed prior to the intervention visit the IPM team may place the traps and return to the house after 3-4 days for the placement of gel bait. The IPM team will count the number of cockroaches caught on the sticky traps and use a vacuum as a cockroach removal tool. The local pest management company, Innovative Pest Management, provides protocolized IPM services for a current study. As many as four IPM visits may occur for persistent or recurrent infestation. If new evidence of mouse or cockroach is seen or reported any time between HV1 and INT 3, the appropriate module will be completed in the home before CV3.

Allergen-proof mattress and pillow encasements will be installed by study staff. These encasements block particles down to 1 micron in size so are optimal for blocking allergens such as furry animal allergens that are found on smaller particles than dust mite and cockroach allergens.

Targeted cleaning will be included in all allergen-related modules. Targeted cleaning will take place at Intervention 1 and 4. For the rodent and cockroach modules, cleaning will focus on removing allergen reservoirs and cleaning areas that have the greatest pest activity, such as the kitchen. For the furry pet and dust mite modules, the targeted cleaning will focus on the child's bedroom with the goal of reducing allergen levels in the bedroom.

IPM Education will focus on counseling participants about storage of food and housekeeping practices aimed at reducing food and water sources for pests. Participants receiving the rodent module will be provided an IPM kit that includes traps and other supplies so that families can implement IPM measures in addition to the professional IPM services that are provided.

Replacement Bedding will be included in all modules. The study will provide bedding (sheets, pillowcases, and comforter) to the participant throughout the study. The child's bedding will be replaced at Intervention 1 and 3 with bedding provided by the study. The participant's bedding will be removed from the bed and replaced with study bedding at Intervention 1. At Intervention 3 the study bedding will be removed and replaced with another set of study bedding. At Home Visit 3 the study bedding will be removed and replaced with the participant's original bedding. All study bedding will be laundered by the JHH laundering facility after it is removed from a home before being deployed to another participant. Families will also be counseled to wash all of the child's bedding in the hot water cycle every 1-2 weeks.

Furry pet and dust mite education will be delivered by study staff. For pets, it will focus on encouraging the family to find the pet a new home or, at the least, to restrict the areas of the home that the pet can be in, particularly the child's bedroom. For dust mite and furry pets, families will be counseled to wash all of the child's bedding in the hot water cycle every 1-2 weeks.

SHS Education will include provision of resources for smoking cessation and tools and support for instituting a home smoking ban.

Air Purifiers will be provided to everyone randomized to the ECS + Medication Group as the targeted community is known to have high levels of $PM_{2.5,}$ PM_{10}, and airborne mouse allergen. Portable HEPA purifiers with the same clean air delivery rate and performance characteristics of the purifiers used in our earlier studies will be used.[12, 14] The purifiers will be suitable for use in rooms up to 17'x10', so will appropriate for use in rooms found in typical Baltimore housing. A random 10% sample of air filters will be monitored using electric current data loggers that record the presence of an electric current every hour in order to estimate air purifier use.

The first ECS module will be delivered between CV1 and CV2. Intervention 2, delivered only to those participants receiving the rodent and/or cockroach modules, will be delivered between CV2 and HV2. If possible, Intervention 3 will be delivered immediately following HV2 on the same day. If this is not possible, Intervention 3 will be delivered prior to CV3. Intervention 4 will be delivered between CV3 and CV4. At intervention visits, education

will be reinforced to participants randomized to the ECS+Medication Group to support the family's efforts in reducing allergen and pollutant exposures.

The Medication Group will receive skin test results at CV0 and educational materials about environmental control practices at CV1. The same educational materials will also be given to the ECS+Medication Group. The Medication Group will be offered the intervention after completion of the study with the exception of bedding being replaced. This visit is to be scheduled within 2 months of their last study visit.

All procedures and tests are part of the research protocol with the exception of study drugs, which are typically covered by health insurance.

b. Study duration and number of study visits required of research participants.

Participants will be enrolled for approximately 7 months. There will be five clinic visits and three home visits over this time period for clinical and home assessments, respectively. There will be up to four environmental intervention visits for participants randomized to the environmental control plus controller medication group. Participants randomized to the controller medication group have the option of having one home visit after completing the study at which they will receive home intervention services that the environmental control plus controller medication group received with the exception of bedding being replaced.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants will not be blinded because it is not practical and impossible to create a sham environmental intervention without exorbitant costs. The study physicians applying the treatment algorithm, which drives the primary outcome, will be blinded to the extent possible. For example, study staff will be trained not to divulge the participants' randomization group to the physician during the clinic visit.

d. Justification of why participants will not receive routine care or will have current therapy stopped. Participants will be asked to stop anti-histamines for approximately 5 days prior to skin testing at the screening visit.since anti-histamines interfere with the skin test results. Otherwise, all participants will receive nationalguidelines-based titration of controller medication and education about asthma management.

e. Justification for inclusion of a placebo or non-treatment group.

Although there are two groups being compared in this trial, there is no group that is not receiving guidelines-based asthma treatment.

f. Definition of treatment failure or participant removal criteria.

A study participant will be discontinued from further study intervention if any clinical adverse event, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

This includes: (1) an asthma hospitalization that results in intubation and (2) a second asthma hospitalization during the course of the study.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants may withdraw consent or be dropped from the study at any time. Every effort will be made to contact the participant by phone to conduct a final telephone interview. Participants will be referred back to their primary care provider (or subspecialist, if receiving subspecialty care) for asthma management.

All participants exiting the study after randomization without having received CV2 will be replaced.

4. Inclusion/Exclusion Criteria

Inclusion Criteria

- Males and females who are 5-17 years of age, inclusive, at the baseline visit
- Have physician-diagnosed asthma at least 1 year prior to the baseline visit, or asthma symptoms for at least 1 year
- Meet criteria for current persistent asthma defined as either:

    1. On a long-term controller medication for asthma, or

    2. Meet NAEPP guideline requirements for persistent disease:)[6]

- Asthma symptoms 3 or more days per week over the past 2 weeks OR
- Nocturnal asthma symptoms at least 3 times in the past month

- Have evidence of uncontrolled disease as defined by at least one of the following:

1. One asthma-related unscheduled visit to an emergency department (ED), clinic or urgent care facility in the previous 18 months
2. One asthma-related overnight hospitalization in the previous 18 months
3. One or more bursts of oral corticosteroids in the previous 18 months

- Reside within a geographic area of the study site so that home visits are feasible. • Have no plans to move within the upcoming 6 months
- Have insurance to cover prescription medications.
- Have a positive skin test (net wheal ≥2mm) to cat, dog, mouse, rat, cockroach, or dust mites or have a positive cat, dog, mouse, rat, German cockroach, or D. farinae-specific IgE test, as quantified using the ImmunoCAP system (≥0.35 kU/L)

Exclusion Criteria

- Lung disease, other than asthma, that requires daily medication
- Cardiovascular disease that requires daily medication, excluding hypertension
- Taking a beta-blocker • Allergy to dairy
- On Xolair < 5 months
- On immunotherapy and has not reached maintenance dose
- Sleeping in another home 4 or more nights/week
- Active smoker defined as a positive urine screen for high levels of urine cotinine
- Unable to access areas of home necessary to conduct extermination • Pregnancy

5. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The intervention being tested is the environmental intervention, but all participants will receive asthma medication based on national guidelines. All will receive a short-acting beta agonist, albuterol, for use as a reliever medication. All participants, at least at the start of the study, will also receive a controller medication, Flovent or Advair or an equivalent alternative medication.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. N/A

Justification and safety information if non-FDA approved drugs without an IND will be administered. NA

6. Study Statistics

a. Primary outcome variable. The primary outcome variable is the treatment step that the participant is assigned at the 6 month clinic visit (see treatment algorithm above).

b. Secondary outcome variables.

Secondary outcomes include: (1) daily inhaled corticosteroid dose, (2) allergic inflammation markers (allergen-specific IgE, FENO, (3) measures of asthma control (days of short-acting beta agonist use, days of slowed activity due to asthma, days of exercise-induced symptoms, days of cough without an upper respiratory infection, nights of wakening due to asthma symptoms), and (4) measures of exacerbations (oral corticosteroid bursts, hospitalizations, emergency department visits, and unscheduled physician visits). Other secondary outcomes include FEV1/FVC, % change in FEV1 after albuterol, and asthma severity, as measured by the CASI.[29]

c. Statistical plan including sample size justification and interim data analysis.

Power Estimate

The power estimate is based on assessment of the primary outcome, treatment step, at 6 months. In the ICAS trial, the ECS resulted in a reduction of 0.8 symptom days/2 weeks within two months of randomization.[13] The authors of the paper make the point that this effect size is similar to that seen with controller medications. In PREACH, the SHS intervention trial, there was an increase of 1.9 symptom-free days/2 weeks at six months in the group receiving air purifiers compared to the control group. This effect, which was observed with air purifiers alone and no other environmental intervention, is also similar in magnitude to low dose, inhaled corticosteroids, which resulted in an increase of 2 symptom-free days/2 weeks compared to placebo among children with persistent asthma (CAMP).[9] With a multi-faceted intervention as proposed for this study, we expect a significantly larger effect size than observed with air purifier deployment alone. In terms of treatment step, low dose ICS is one "step-up" from no controller medication, which reflects the difference in controller medication requirement that our proposed study is powered to detect. Further, a 1 step reduction in controller medication requirement would also be the point at which an ECS would likely be cost effective. For example, in the ICAS trial,[13] the intervention, which was effective for two years, cost approximately $1500, similar to the cost of a one year supply of low dose ICS. There will be 7 possible treatment steps (Table 6) and, based on the distribution of participants across treatment steps in other studies, we will assume a mean treatment step of 4.0 at baseline among participants in both groups and have estimated the power to detect a difference of 1 treatment step between the two groups, with a standard deviation between 1.5 and 2. With a sample size of 200, and assuming alpha=0.05, we will have a power of 0.94 to detect a difference of this magnitude. With a drop-out rate of ~12%, there will be a power of 0.90. (Table 6)

Table 6. Power Estimates

Treatment step difference	SD	Power for n=200	Power for n=175
0.75	1.5	0.94	0.90
	2.0	0.75	0.69
1.00	2.0	0.94	0.90
	2.5	0.80	0.74

Analysis Plan

The primary outcome will be the treatment step that is assigned at the final clinic visit at six months. The six month time point has been chosen because successful ECS trials have observed an effect by six months, but an effect may not be observed before this time because it takes several months for indoor allergen levels to fall after implementing an environmental intervention. The secondary outcome will be total daily ICS dose assigned at this same visit, expressed in milligrams. The primary analysis dataset will be an intent-to-treat (ITT) dataset and will include participants with six month outcome data collected, regardless of whether they completed all of the ECS activities. A per-protocol analysis will also be performed and will be performed on the dataset of participants with six month

outcome data who completed at least one intervention visit (one IPM visit or for the Medication Group, receipt of ECS educational materials). Exploratory data analysis for both Aims 1 and 2 will include compilation of descriptive statistics to detect any outliers or discrepancies in data and to compare baseline characteristics and demographics between ECS+Medication and Medication Groups. Continuous variables will be summarized using means, medians, standard deviations, ranges, and interquartile ranges. Continuous variables will be analyzed using non-parametric approaches or will be transformed to meet assumptions of normality required for parametric statistics. Categorical variables will be tabulated. The percent of participants who complete the study, losses to follow-up, missed visits, and reasons for discontinuation will be presented.

The primary outcome will be the participant's assigned treatment step at the six month clinic visit (as described above). Secondary outcomes include: (1) daily inhaled corticosteroid dose, (2) allergic inflammation markers (allergen-specific IgE, FENO,), (3) measures of asthma control (days of short-acting beta agonist use, days of slowed activity due to asthma, days of exercise-induced symptoms, days of cough without an upper respiratory infection, nights of wakening due to asthma symptoms), and (4) measures of exacerbations (oral corticosteroid bursts, hospitalizations, emergency department visits, and unscheduled physician visits). Other secondary outcomes include FEV1/FVC, % change in FEV1 after albuterol, and asthma severity, as measured by the CASI.[29] We will subtract baseline levels of the treatment step from the step assigned at the 6 month CV to assess the within-person change in treatment step over time. Differences over time in the intervention group will be compared to those in the control group using a generalized linear modeling approach and a significance cutoff of 0.05. Assessment of significance adjusting for multiple comparisons will be done using the method of Benjamini and Hochberg.[37] Regression models will be used to adjust for potential confounders and to test for interactions with potential effect modifiers. A similar analytic approach will be used for other clinical and inflammation outcomes, with appropriate statistical tests and models for the different types of outcome variable data, such a Chi-Square test and logistic regression for dichotomous outcomes.

Potential confounders will be explored by examining any differences between the intervention and control groups and also assessing the association between the potential confounders at baseline and at the final study visit. In addition, potential confounders will be included in the models to determine the impact the variables have on the relationship between group assignment and the outcome. Some specific confounders that will be carefully examined include baseline allergen and pollutant levels, treatment step at baseline, and season. Potential effect modifiers, such as baseline pollutant and allergen levels, baseline asthma severity, baseline asthma control, baseline lung function, and number of positive skin tests, will also be examined by stratifying analyses and creating an interaction term to include in the final models. Analyses will be stratified by these potential response predictors and interaction terms will be included in models to determine of any of these factors predict responsiveness to the intervention.

To measure the change in home airborne particulate matter ($PM_{2.5}$ and $PM_{2.5-10}$) and indoor allergen concentrations (cat, dog, mouse, cockroach, and dust mite) among study participants. Distributional properties of baseline levels of pollutants ($PM_{2.5}$ and $PM_{2.5-10}$) and allergens will be assessed using histograms and boxplots and any necessary transformations to these variables will be conducted to obtain approximately Normal distributions. We will subtract baseline levels of these exposures from levels recorded 6 months post-randomization to assess the within-person change in exposure over time. Differences over time in the intervention group will be compared to those in the control group via standard *t*-tests using a significance cutoff of 0.05. Assessment of significance adjusting for multiple comparisons will be done using the method of Benjamini and Hochberg.

To evaluate the role of bacterial communities and *S. aureus* colonization on asthma morbidity, we will perform exploratory data analysis to identify outliers and missing data, and to generate descriptive summaries of multiple outcome variables related to asthma morbidity. The primary predictive variable will be *S. aureus* colonization. We will test *S. aureus* association with asthma outcomes over multiple visits using random effects models. In order to adjust for potential confounders, such as child demographic characteristics, *etc.*, we will construct multivariate random effects models that account for repeated assessment of the outcomes and time-varying covariates. For bacterial community analysis, we will compare taxonomical relative abundances using the Wilcoxon rank-sum test. Accounting for clustering within home and host, we will identify the influence of demographic and other factors on

microbial composition by calculating the weighted and unweighted UniFrac and the non-parametric ANOSIM (ANalysis of SIMilarities) test.

d. Early stopping rules.

The protocol may be halted by the DSMB, IRB or Sponsor upon review of SAEs.

7. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Questionnaires

The risk of the questionnaire is breach of confidentiality.

Blood draw

The risk of blood drawing is discomfort, bruising, lightheadedness, and rarely infection.

Lung function and exhaled nitric oxide testing

The risk of lung function and eNO testing is the discomfort of exhaling forcefully, light-headedness and occasional minor chest soreness.

Home visits

The risk of the home visit for collection of environmental data is breach of confidentiality.

Skin testing

The risk of skin testing is primarily the discomfort from any positive skin tests, which would result in wheal and flare responses and pruritus. Approximately 2-3 in 10,000 skin prick tests results in allergic symptoms away from the site of the skin testing, such as sneezing, rhinorrhea, or rash.[38, 39] Very rarely, an individual who experiences this type of reaction may develop life-threatening symptoms such as persistent coughing or wheezing. A study published in 1987 reported six fatalities from skin testing since 1945.[39] From 1985-1989 there were no fatalities from skin testing reported,[40] and one fatality was reported from 1990-2001.[41]

Buccal Cell Collection

There is no known risk associated with the collection of buccal cells using swabs such as this Q-tip like device.

Copan e-swab™ and Catch-All™ sample collection

There is little known risk associated with collection of microbial cells from the nares, oropharynx and skin using swab devices. Some participants may experience a gag reflex with oropharyngeal sampling.

Nasal Mucus Sample Collection

There is no known risk associated with the collection of a nasal mucus sample using a nasal spray and blowing the nose.

Rodenticides

Rodenticides are long-acting anticoagulants and there is a risk of developing a coagulopathy with intentional ingestion. There have also been case reports of accidental ingestion of these products resulting in coagulopathy.[42, 43] Several prospective studies of accidental rodenticide ingestion in children indicate that almost all accidental ingestions can be managed by observation at home since they rarely result in coagulopathy. In one series, among more than 200 children with reported

accidental ingestion of superwarfarin, two patients had an INR of 1.5 or greater, both of whom were asymptomatic.[44] In another series, the National Poisons Unit for London reported no serious adverse outcomes over a five year period, during which they received an average of 200 reports per year.[45] Of 542 reports of accidental ingestion by children to a US poison control center, follow-up coagulation laboratory tests did not detect any significant coagulation abnormalities, no child developed bleeding complications, and no child required or received vitamin K.[46] For the purposes of this study, rodenticides will be used by licensed exterminators who will be trained specifically on procedures for the MAAIT. Rodenticide will only be placed in areas that are not accessible to children or pets. Specifically, rodenticide will be placed in holes and cracks, which will then be sealed to prevent extrusion of the rodenticide into the home or access to the rodenticide by children or pets.

Pesticides for cockroaches

The primary insecticide for cockroaches will be Advion (indoxacarb 0.6%) gel bait, which has been highly successful in cockroach abatement. A search of PubMed revealed a few case reports of methemoglobinemia and renal failure in adults who intentionally ingested the pesticide in suicide attempts.[47-49] The Material Safety Data Sheet indicates that: "based on animal testing, no biologically significant effects are expected from skin or eye contact or by ingestion" (http://www.syngentacropprotection.com/pdf/msds/advion cockroach gel bait 11012013.pdf, accessed 06/17/2014)). To minimize risks, bait will be applied in areas targeting cockroach infestation and in the smallest quantities to achieve an effect and will not be placed in areas easily accessible to children and pets.

Cleaning agents and caulking agents

Commercially available, non-bleach cleaning agents (e.g. 409®, Fantastik®) will be used during the cleaning that occurs during the first and last intervention visits. Commercially available foam caulking agents (Pur-fill®) will be used to seal holes and cracks during the IPM visits. Both of these agents contain potential irritants that could cause asthma symptoms. The risk of developing asthma symptoms serious enough to require emergency medical attention is very small. The cleaning agents will be used as directed by the manufacturers. The caulking agents will be used as directed by manufacturer instructions.

Flovent® Diskus®, Advair™ Diskus®

Flovent® Diskus®, and Advair™ Diskus® includes an inhaled corticosteroid. The risks include upper respiratory tract infection, throat irritation, sinus infection, upper respiratory inflammation, rhinitis, a fungal infection inside your mouth, nausea and vomiting, gastrointestinal discomfort, viral gastrointestinal infection, non-specific fever, viral infection, viral respiratory infection, cough, bronchitis, headache, muscle injury, musculoskeletal pain, and injury. Rinsing after taking this medicine may help reduce some of these side effects. At high doses, children taking inhaled steroids may grow more slowly. This is usually temporary.

Advair™ Diskus®

Advair™ Diskus® contains a long acting beta agonist (LABAs). The risks include diarrhea, nausea, asthma exacerbation, lung infections, anxiety, fever, dizziness, difficulty sleeping, and chest pain. There is a rare risk of asthma-related death. This study will follow black box guidelines by using LABAs with inhaled steroids and only when you are not adequately controlled on inhaled steroids.

Albuterol

Albuterol is a short-acting beta agonist. The risks include increased heart rate and blood pressure, nausea, headache, and a jittery or nervous feeling. These symptoms usually end within one hour.

Prednisone

Prednisone is an oral corticosteroid. It will only be used if you develop asthma symptoms that are not controlled by albuterol. Oral corticosteroids can cause hoarseness, sore throat, and yeast infection

of the mouth or throat if taken in high doses for long periods of time. They can also cause effects on the body such as weight gain, growth delay, bruising of the skin, cataracts, and diabetes. These effects are more likely if the medicine is taken at very high doses for long periods of time. These side effects are not likely in this study because of the length of time (typically 4-5 days on any occasion) that oral corticosteroids will be taken.

The following medications will only be used if the above medications are not covered by insurance:

Pulmicort Flexhaler® is an inhaled corticosteroid. The risks include weakness, tired feeling, nausea, vomiting, low blood pressure, skin rash, hives, swelling, breathing problems, higher chance of infection, wheezing, worsening asthma symptoms, headache,, sore throat, rhinitis, stuffy nose, chest pain, anxiety, low bone density, glaucoma, cataracts, slow growth or a fungal infection inside your mouth, Rinsing after taking this medicine may help reduce some of these side effects.

QVAR® is an inhaled corticosteroid. This risks include weakness, tired feeling, nausea, loss of appetite, skin rash, wheezing, worsening asthma symptoms, headache, dryness in mouth, nose or throat, hoarseness, or a fungal infection inside your mouth, Rinsing after taking this medicine may help reduce some of these side effects.

Flovent® HFA is an inhaled corticosteroid. The risks include weakness, tired feeling, nausea, vomiting, low blood pressure, skin rash, hives, swelling breathing problems, higher chance of infection, wheezing, worsening asthma symptoms, headache, dryness in your mouth, nose, or throat, stuffy nose, sinus pain, cough, hoarseness or a fungal infection inside of the mouth. Rinsing after taking this medicine may help reduce some of these side effects.

Asmanex® is an inhaled corticosteroid. The risks include skin rash, hives, swelling breathing problems, higher chance of infection, wheezing, worsening asthma symptoms, low bone density, glaucoma, cataracts, slow growth, or a fungal infection inside of the mouth. Rinsing after taking this medicine may help reduce some of these side effects.

Advair® HFA
The risks include rash, hives, swelling of face, mouth, or tongue, breathing problems, increased blood pressure, fast and irregular heartbeat, chest pain, tremor, nervousness, loss of energy, change in sugar or potassium levels, or white blood cells, higher chance of infection, low bone density, glaucoma, cataracts, slow growth, throat tightness, throat irritation, hoarseness, voice changes, headache, dizziness, nausea and vomiting.

Symbicort® is a combination inhaled corticosteroid and long acting beta agonist. The risks include palpitations, cheat pain, rapid heart rate, tremor, or nervousness, a fungal infection inside your mouth, higher chance of infection, low bone density, glaucoma, cataracts, and slow growth. Rinsing after taking this medicine may help reduce some of these side effects.

Dulera® is a combination inhaled corticosteroid and long acting beta agonist. The risks include inflamed nose, throat, or sinuses, headache, increased wheezing, rash, hives, swelling of face, mouth, or tongue, breathing problems, loss of energy, change in sugar or potassium levels, higher chance of infection, low bone density, glaucoma, cataracts, and slow growth.

b. Steps taken to minimize the risks.

The risk of breach of confidentiality will be guarded against by using unique identifiers for participants and labeling all specimens and data with the identifier rather than name. Likewise, databases will only use unique identifiers with the exception of one database that will contain the tracking and contact information for the

participants. All databases will be kept on a network drive, and permissions for this drive can be controlled to allow only study staff to have access to the databases. The drive is backed up twice daily. Only study staff trained in phlebotomy will perform venipuncture, and the questionnaires, spirometry, eNO, and urine collection for cotinine will be collected by a trained research assistant. Home visits and collection of environmental samples will be collected by a trained research technician. Extermination procedures will be performed by a trained and licensed pest exterminator. Skin testing will be supervised by the Study Coordinator or PCRU nurse who will have direct access to the study physician. Appropriate medications, including antihistamines and epinephrine will be immediately available during all of the skin testing procedures. In addition, a short acting beta agonist will be available.

An independent Data Safety Monitoring Board (DSMB) will be populated by experts in clinical trials, data and safety monitoring, and asthma. The DSMB will review the protocol prior to beginning the trial. In addition, the DSMB will meet annually to review accrual and adverse events.

The DSMB will review any event as requested by the Investigators or the sponsor. They will review the study annually, including accrual and adverse events and submit a report following their meeting. Related adverse events and serious adverse events, whether deemed related to study procedures or activities or not, will be tracked.

There will also be weekly meetings of the investigators and study staff, which will include an update of all related adverse events and drop-outs. All serious adverse events will be reported in an expedited manner to the IRB. All unexpected and related serious adverse events will be reported to the DSMB per their request.

c. Plan for reporting unanticipated problems or study deviations.
Unanticipated problems or study deviations will be reported to the IRB and DSMB in an expeditious manner, in adherence with institutional policies.

Adverse events will be documented on an individual adverse event log for each participant. An adverse event form will be used for reporting all related adverse events. An additional form will be required for serious adverse events to collect additional information. Information that will be documented includes a brief description of the event, onset and duration of the event, severity/grade of the event, resolution status of the event, and relatedness to the study procedures. Any medical intervention will also be documented.

A serious adverse event (SAE) is defined as any adverse experience that suggests a significant hazard, contraindication, side effect, or precaution. This includes, by may not be limited to, any of the following events:

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of the therapy whether or not considered treatment- related, must be reported.
2. Life-threatening: Any adverse therapy experience that places the subject or subjects, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more serious form, might have caused death).
3. Inpatient hospitalizations or prolongation of existing hospitalization. 4. Persistent or significant disability or incapacity
5. Congenital anomaly or birth defect.
6. An event that required intervention to prevent permanent impairment or damage.

For reporting purposes only, when a participant is hospitalized for an asthma exacerbation, the date of onset of the exacerbations will be the date of hospital admission and the date of resolution will be the discharge date.

For the purposes of this protocol, a pregnancy is considered an SAE and will be reported and followed until resolution of the pregnancy with the exception of participants in the Household Asthma Sub study. Pregnancy is not an exclusion for these participants.

d. Legal risks such as the risks that would be associated with breach of confidentiality.
The primary legal risk is breach of confidentiality. See above for description of how this risk will be minimized.

e. Financial risks to the participants.
Prescription drugs will not be covered by the study. Prescription drugs are typically covered by health insurance. Participants are responsible for medical care if injured in this study.

8. Benefits

a. Description of the probable benefits for the participant and for society.

The potential benefits for the study participant includes receiving an assessment of allergic sensitivities, lung function, exhaled nitric oxide, assessment of home environmental exposures, room air filters, allergen-proof mattress and pillow encasements and IPM. This knowledge will impact the way physicians provide care for inner-city asthma patients, and will impact policy decisions regarding environmental interventions to reduce home exposures that may trigger asthma symptoms. This information will directly impact the medical care provided to this patient population.

The findings from the proposed trial may directly impact patient care and policy. This proposed trial will answer a pivotal question because if ECSs do not provide additional benefit in the context of treatment with controller medication, the role of ECS in asthma management should be downgraded. On the other hand, if ECSs do indeed reduce controller medication requirements, greater emphasis should be placed on the importance of ECSs in asthma management, studies should be conducted to identify best ECS practices, and policies should be changed to require third party payers to cover ECS costs.

9. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will receive $40 for each clinic visit completed plus an extra $10 if they bring their medications to the visit (x5). Participants who do not meet eligibility requirements at clinic visit 1 will not be able to complete the visit but will be paid $10 for the visit. At each clinic visit the child will receive a toy or gift card valued at $10. Participants will receive $25 for each home visit (x3). Participants will receive an additional $5 per pet per home visit for sampling of pets. Transportation to and from the clinic visits will be paid for by the study.
Participants who use the pest hotline and allow pick-up of fresh rodents will be compensated $20.

10. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Participants will be prescribed asthma medications during this study. Typically these medications are covered by health insurance and participants are only eligible if they have insurance.

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