Title of Study: Personalized treatment algorithms for difficult-to-treat asthma: Bench to Community

Short title of Study: Breath Warriors

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1. ABSTRACT

Asthma is a common, complex and costly chronic condition both locally and across the U.S. Moreover, asthma is heterogeneous in terms of treatment response and natural history. This heterogeneity contributes to the difficulty in both studying and treating asthma. This is a pilot study to improve asthma outcomes in 30 youths with difficult to treat asthma with ongoing symptoms and healthcare utilization despite medium to high doses of inhaled corticosteroids. We will identify difficult to treat (DTT) asthmatic children at CCHMC and in the community by leveraging key partnerships and efforts that are already in place with Cincinnati public schools, Cincinnati Health Department and community practices. Although CCHMC has participated in several initiatives and successfully reduced ED visits and hospitalizations among Medicaid-insured asthmatic children, we did not explore the biologic mechanisms underlying these DTT patients. Asthma heterogeneity in both disease pathophysiology and treatment response contributes to the difficulty in both studying and managing asthma. In order to begin to develop personalized

algorithms for patients, we need to model novel biomarkers and other factors that contribute to individual differences in asthma outcome and test personalized treatment strategies. Furthermore, our community partners will be involved in key design elements of this project: engagement of patients, increasing community awareness, and dissemination of the progress and results of the study back to the community.

2. PURPOSE OF STUDY:

The purpose of this project is to achieve the best possible health outcomes for the most at-risk children with asthma through synergistic integration of clinical care, basic, translational and community-based research efforts. This is a pilot study to improve asthma outcomes in 30 youths with difficult to treat asthma with ongoing symptoms and healthcare utilization despite medium to high doses of inhaled corticosteroids. We will identify DTT asthmatic children at CCHMC and in the community by leveraging key partnerships and efforts that are already in place with Cincinnati public schools, Cincinnati Health Department and community practices. Our community partners will be involved in key design elements of this project: engagement of patients, increasing community awareness, and dissemination of the progress and results of the study back to the community.

3. BACKGROUND:

Asthma is a common, complex and costly chronic condition in the U.S., resulting in nearly 2 million acute care visits and $56 billion in overall costs each year (Akinbami 2012). Of these patients, 5-20% have poorly controlled asthma accounting for nearly 50% of all asthma-related expenditures (Pakhale 2011). Both nationally and locally, minority and disadvantaged children have the highest prevalence of asthma and the greatest disparities in asthma morbidity and mortality. Within Hamilton County, over 36,000 children have asthma, >14,000 of whom are Medicaid-insured with a 10 fold higher rate of hospitalization. Moreover, asthma is heterogeneous in terms of treatment response and natural history. This heterogeneity contributes to the difficulty in both studying and treating asthma. We have already developed successful, collaborative programs (as part of SP2015) with General and Community Pediatrics, community agencies, Hospital Medicine, Pulmonary Medicine to reduce ED visits and hospitalizations among Medicaid-insured asthmatic children, sustaining a >20% reduction in ED visits and hospitalizations since 6/2015. Although this work targeted high-risk patients, we did not explore the biologic mechanisms underlying these difficult to treat (DTT) patients. Asthma heterogeneity in both disease pathophysiology and treatment response contributes tothe difficulty in both studying and managing asthma. In order to begin to develop personalized algorithms for patients, we need to model novel biomarkers and other factors that contribute to individual differences in asthma outcome and test personalized treatment strategies. Our proposal is highly innovative in that it will provide a basis for molecular sub-classification of the DTT asthma endotype and provide a foundation and framework for the development and implementation of multi-modality treatment strategies specifically designed for this high-risk/cost subgroup. We have the opportunity to become the national/international leader in pediatric asthma activities spanning discovery to new treatments and novel health delivery systems.

4. STUDY DESIGN

We will conduct study visits in the Schubert clinic to determine and quantify known molecular, genetic, genomic, epigenetics, immunologic, and exposure biomarkers that will help elucidate molecular disease endotype within the DTT phenotype (Figure 1). This information will be used along with clinical, psychosocial, and adherence data to develop

a personalized treatment plan. We will track disease outcome metrics including exacerbations, symptom-free days, and a validated asthma composite control score to determine the effectiveness of this personalized approach (summarized in Figure 1).

A number of interventions will be incorporated based on information collected on questionnaires on personal and family medical history, history of environmental exposures, previous and current residential and school addresses, depression, anxiety, dietary intake, adherence, medical literacy, and perceived quality of life, medical visits, use of a commercially available inhaler cap monitoring sensor, a mobile software management platform that tracks adherence of asthma medications, mobile based telehealth adherence problem-solving interventions, biomarker assays and home trigger assessment and remediation.

This proposal is funded through a CCHMC ARC award.

5. DURATION:

Duration for the participants will be 12 months. We will continue to follow asthma outcomes via the patient's medical record for an additional 12 months. Participants will be enrolled in the study during the 24 months of the project. If additional funds are awarded, the enrollment period may be extended to a third funding year. Data analysis will be performed 6 months after the last participant completes the project.

6. SELECTION & RECRUITMENT OF PARTICIPANTS:

A. Number of participants

Patient Population*:* 30-50 6-17 year old children with uncontrolled moderate-severe persistent asthma without significant chronic disease other than allergic disorders.

B. Inclusion/Exclusion criteria

Inclusion

- age 6-17 years; history of provider-diagnosed asthma;
- Meets one of the following definition for NAEPP guidelines uncontrolled moderate persistent asthma or severe persistent asthma in the past 12 months:
    - NAEPP step 3-4 with one of the following criteria in the past 12 months:
        - two ACT scores <20
        - ≥ 1 UC/ED visit or hospitalization for asthma
        - ≥2 prednisone bursts
    - NAEPP step 5-6
- Current health insurance coverage at enrollment. This will be verified at V1 at the registration desk. If the family loses insurance during the study, the patient will be referred to the pulmonary social worker and CCHMC financial office for assistance.
- Reside at a primary home on average 5 out of 7 days a week.
- Primary home is within a 40 mile radius of Cincinnati Children's Base location or PI's discretion.

Exclusion

- Received biologic therapy 6 months prior to enrollment
- Received systemic steroids 6 weeks prior to enrollment
- active chronic disease apart from asthma or allergic disease
- co-morbid lung disease
- dependence on immunosuppressive drugs for a condition other than asthma
- Participant is pregnant
- Has a severe bleeding disorder
- Has significant developmental disability
- Share a bedroom with a currently enrolled Breath Warriors study participant

C. Recruitment

- We anticipate that about 30% of these children will be identified by our community partners in CCHMC primary care clinics, community based primary care practices, community recreation centers, or Cincinnati Public Schools. We anticipate that the remaining 70% of children will be identified during CCHMC hospitalizations, Emergency Department or pulmonary or allergy sub-specialty clinics for asthma-related visits.
- Given the relationship of the CCHMC Asthma Center with Cincinnati Public Schools (CPS) and the Cincinnati Health Department in our ongoing quality improvement work, the study investigators have contacts with the school staff and school nurses associated with Cincinnati Public schools, community recreation centers, and primary care providers. As part of this work, study investigators have also assisted the school nurses to screen children with asthma to identify those with uncontrolled asthma and help the nurse's contact families to encourage them to establish or connect with an existing medical home to schedule an asthma visit and to obtain asthma medication.
- We have access to eligible participants from several sources: over 2000 children that attend the participating CPS or children cared for at the CCHMC ED or hospital units (~4000 per year). The Ohio Pediatric Asthma Repository (OPAR, IRB protocol #2014-1003, PI Khurana Hershey) and the Greater Cincinnati Pediatric Clinic Cohort (GCPCR, IRB #2010-0438. PI Khurana Hershey) are also potential recruitment sources. We anticipate that participants will have similar demographic characteristics as our current CPS population (18% Caucasians, 73% Black, 5% More Than One Race) that is comprised of over 70% of participants from low-income families.
- The children will be recruited by one of the following methods: 1) During the asthma screening process at the school as part of our QI work, 2) a school or community center flyer, 3) CPS-CHD school nurse,) during a CCHMC clinic or inpatient visit for asthma, 5) a community primary care provider, or 6) health fair at a community site. Once a child is identified, and has verbally agreed to be contacted from one of these sources, the study team will contact the family and screen for eligibility using a phone script and eligibility checklist.

  We will utilize several successful strategies employed in our past research to retain families. We will implement the following; (1) stress confidentiality, (2) gather detailed information regarding names, addresses, and phone numbers of people who might know where the family is living in case they lose contact with the study, (3) adequate

incentives, (4) provide email, phone and/or text reminders of upcoming study visits, (5) frequent mailings of birthday cards, holiday cards, and quarterly newsletters, (6) letters mailed to the home asking families to contact study staff to reschedule missed appointments, (7) home-visits to confirm that the family continues to reside at the available address for those who lack telephone service, and (8) searching publically available resources including social-media websites. The study consent form contains information that we plan to contact them by phone call, text, email or Facebook.

Because this is a long-term study, with extended periods of time between research - related interactions, maintaining the cohort will be a challenging element of completing the research. In order to facilitate the retention of the cohort, specific information will be obtained during the first research encounter (and updated at all subsequent encounters). Although critically important to the successful completion of the research, if a participant expresses concern and or refuses to provide this information they will not be excluded from the research.

The information collected on data collection form, the contact form, will be used for this purpose.

Once collected this contact information will be stored in a separate secure database separate from the participants research-related information and will not be shared with additional participating sites, external research coordinating centers or as a part of the main study database.

The data and/or biological samples that are collected will also become part of the Greater Cincinnati Pediatric Clinic Repository and stored indefinitely**.** The samples may be used by researchers at Cincinnati Children's Hospital Medical Center or at other institutions for asthma, allergy and immune system related research. All investigators must get local Institutional Review Board approval prior to requesting data and/or samples from this repository if applicable. If participant samples and/or data are released to institutions other than Cincinnati Children's Hospital Medical Center, we will remove any PHI.

The research team will attempt to re - contact the lost to follow - up participant. Once contact is re - established, the participants will be reminded of the research study and that they voluntarily agreed to participate, interest in continued participation will be verbally confirmed and documented and the participant will return to active study participation as appropriate based on their status/time point in the research.

In the consent/assent form, participants and parent/guardian will be told that, we will obtain information that will help us find them in case they move. This information includes several demographic details, various phone numbers, and the names and addresses of close relatives or friends who will know of their whereabouts. Participants will be informed that we will use this information to locate them and that their information will be secured and will not be shared with anyone outside the study team. During the consent/assent, when participants are supplying the "demographic information" we will reiterate the fact that we will use this information to find them in case we lose track of their whereabouts. They will be reminded that we will not share this information with anyone outside the study team. Finally, participants will be informed that they may be eligible for follow-up assessments after the study has been completed and we will use this information to locate them in order to let them know of their eligibility for future research.

D. Vulnerable Populations

- For participants under 18 years of age, additional efforts will be made to protect this vulnerable population. Assent will be obtained after age appropriate explanation of the study. The participant is informed that participation in research is voluntary and that they may decline or withdraw at any time for any reason independent of their parent/guardian. Assent will be reaffirmed before study procedures are performed. They will be informed that participation in the research will not affect their clinical care in the community or CCHMC.

7. PROCESS OF OBTAINING CONSENT:

If the parent and child/adolescent state they are interested in the study on the screening phone call or during a health fair, the team will schedule a visit at CCHMC. At the first visit, we will review the informed consent document and obtain parent/legal guardian(s) consent and assent from the child/adolescent. The consent form includes a modified language from the CCHMC standard consent used to obtain participant consent for a CCHMC adherence telehealth visit.

We are requesting a waiver of written consent for the screening phone call that will include review of medical history information and inclusion/exclusion criteria. We may also mail them the ARC New Visit Form prior to V1 and have the family bring it to V1. An IRB approved phone script will be used. We are asking for a waiver of written HIPAA authorization to identify potential participants by review of school clinic health data records for inclusion/exclusion criteria and contact information/phone number. Signed HIPAA authorization will be obtained at the time of written informed consent.

- The subject or the subject and his or her parent will be given the consent for the study and it will be reviewed and time given for questions. The subject will sign the assent or consent after all questions are answered and a signed copy of the consent form will be given to the subject to keep. The subject will be informed that

this research is voluntary and that they are able to withdraw at any time. No study related procedures will be done prior to consent being signed. Subjects that reach the age of 18 years during the study will be consented by a study coordinator via a phone call or at next scheduled home visit. Participants may e-consent by using the CCHMC eConsent Management program or equivalent. Research staff will describe the study and inform the potential participantthe required elements of consent, informing potential participant that participation is voluntary and they are free to withdraw at any time. Participants that choose to do the e-consent will have the opportunity to review the eConsent form and talk to research staff. The potential participant will log in to the eConsent application with an identification number and password given to him/her by study staff. After reading through the form (i.e. scrolling to the bottom), they will have an opportunity to check a box stating that they agree to provide their consent / parental permission / assent. There will also be fields for full name and password. Once they have typed their full name and re-entered their password, they will be able to submit. A copy of the "signed" form will be emailed to the study staff. If the participant provides an email address, they can have a copy emailed to them as well.

If a consent/assent form is updated and requires a new signature, coordinators will go over the changes via either a scheduled monthly phone call or scheduled study visit (depending on which visit occurs first) and participants and guardians may be reconsented by either eConsent (as stated in the section above) or by signing a copy of the consent/assent either in person or sent through the mail. Participant's and guardians will be given ample time to read through the new consent/assent and will be able to call and ask questions etc. once they have been able to read through the consent/assent.

For participants under age 18, age of assent will be determined by the IRB and those assenting will sign after all questions are answered.

For non-English speaking participants

Because this is a small pilot and heavily dependent on English fluency for teleconference interviews and questionnaires, only participants who are fluent in English will be enrolled. If a parent is non-English speaking, the PI will determine if the subject can be enrolled based on subject's fluency. If a non-English speaking parent will be giving Parental Permission, the research team will use a short form consent process as per CCHMC SOP 41-1.8. The approved long consent form will serve as the summary of the research.

8. STUDY PROCEDURES:

See Appendix A.

The study length is 12-15 months. 30 participants will be enrolled over a 9 month period. Propeller and TreatSmart program screenshots are located in Appendix B and C.

CCHMC Visit 1 (V1)- Baseline Medical Visit: This visit will be conducted at CCHMC.

The coordinator will consent the parent/legal guardian(s) and (if applicable) obtain assent from the child/adolescent. Baseline questionnaires will be completed by a parent/guardian and the participant, and the study visit procedures will be explained by the study coordinator.

The study coordinators will conduct this visit. The participant will complete an Asthma Control Test (ACT), and the study coordinator will assist the participant in completing the TreatSmart program on a CCHMC secured laptop. The TreatSmart software web-based program, developed at CCHMC and hosted on a CCHMC secure server, will be used to determine the participant's CASI score and will determine the level of asthma severity/control the participant has. The program also makes an initial treatment recommendation based on the National Asthma Education and Prevention Program (NAEPP asthma guidelines), if the participant's asthma meets the definition of persistent asthma, and if their treatment dose should remain the same or be changed based on their level of control. This program will also produce a visit summary and asthma action plan. In the event that the TreatSmart program is not working or other issues arise, the Treatsmart content may be completed on paper. The TreatSmart program takes approximately 10 minutes to complete.

After the TreatSmart program is completed, one of the pulmonary or allergy specialist investigators (Guilbert, Durrani, Kercsmar, McDowell, Khurana Hershey), pulmonary or allergy fellows, or asthma research or pulmonary nurse practitioner will perform a physical exam, review PFT report, review the TreatSmart program visit summary and treatment recommendations, and make a final decision of the level of asthma control and asthma medication needed. The visit summary, asthma medication recommendation and asthma action plan from the medical visit will be physically given to the participant and family. These documents in the form of a letter will be sent to the child's school nurse (if the school nurse referred participant to the study) and primary care provider by the study team.

Prescriptions for asthma medications and inhaler spacers will be written by the study physician and offered to be sent to a home delivery or routine pharmacy depending on the family's preference. The study coordinator will also provide basic asthma education to the participant.

Procedures done at these visits include:

- Asthma and Allergy related Questionnaires, ACT, Treat Smart Research clinic visit (CCHMC T building) with medical evaluation
- Download Jabber app on parent/participant smartphone/iPad (or CCHMC provided iPad) and instruction on how to use app for future visits.

Biological Samples and Measurements:

- Pulmonary Function Testing (PFT) / Spirometry: Children may be asked to undergo PFT. PFTs will be conducted according to ATS criteria by personnel who have completed a spirometry training course. A spirometer will be used that meets ATS standards. Some asthma medicines will be stopped from 8 to 24 hours before the PFTs to meet ATS standards. The participants and their families will be instructed on which medicines not to take before the test and informed that stopping asthma medicines may make their asthma symptoms worse. They will also be instructed that if the child has asthma symptoms, they should NOT stop taking their medicine, and we will reschedule the test. If the child starts to have asthma symptoms after stopping the medicine, we will recommend that the child resume the medicines as prescribed. Nose clips and disposable bacterial/viral mouthpieces will be used. The children will be coached through each standard forced expiratory maneuver in a seated position. A post-bronchodilator test will be obtained. The children will be given up to 6 puffs of albuterol and lung function will be repeated to look for reversibility per ATS guidelines. The most common risks associated with albuterol use is a high heart rate or lightheadedness.
- Skin Prick Allergy Testing: Skin prick allergy testing on the participants' forearm or back by a trained professional will be performed on participants. The test will include the following antigens: dust mite, cat, dog, cockroach, mold mixes (2), ragweed, grass mixes (2), tree mixes (2) and foods. Participants having allergy skin prick testing. The results of these tests will be mailed to the parent/guardian and participant after the visit to share with their primary care physician. The results will be used to indicate allergen sensitization. Because antihistamines will interfere with the skin testing, the parents/guardian may be asked to refrain from

giving the child any antihistamines in the week before their visit. If the child requires antihistamines in the week before the study visit, the visit will be rescheduled.

- Blood: The amount of blood drawn may not exceed 50 ml or 3 ml per kg whichever is lesser, and collection will not occur more frequently than 2 times per week. Participants will be asked if they have had any blood drawn or plan to have any blood drawn within the 24-hour period of the research draw. Blood will be collected by study coordinators or by trained phlebotomists at the CCHMC Test Referral Center or the Schubert Research Clinic, provided that this amount is safe for the participant. If the age or condition of the patient limits the amount of blood that can be collected, this may be omitted or a smaller amount may be collected that is more appropriate. A numbing agent may be used to decrease the pain associated with venipuncture if requested by the parent/guardian. Blood may be used to isolate nucleic acid or proteins using standard protocols. Whole blood, serum, plasma or other blood components like peripheral blood mononuclear cells (PBMCs) may be obtained from the blood by the CTRC Laboratory, the CCHMC Clinical Laboratory, or an investigators' laboratory and either used immediately or stored for future studies. The blood samples may be sent to Stanford University for analysis by mass cytometry. Blood may be evaluated for biomarkers of inflammation, oxidative stress or disease, vitamin D, complete blood count and differential, and/or specific IgE and total IgE using standard techniques. In some cases, blood may be used to make immortalized or virus-transformed cell lines and frozen and stored in the laboratory. Blood components or cells lines may be used to identify immunological and environmental markers of exposure or allergic disease including, but not limited to evaluation of cellular responses, interleukins, cytokines, fluorescent plasma oxidative stress products. Genetic testing related to immune response, inflammation, oxidative stress, allergic, environmental exposures, or asthma related diseases may also be performed. The results of the vitamin D level, IgE and complete blood count and differential will be reviewed by one the study physicians. If abnormal and felt to be clinically relevant, it may be repeated at the physician's discretion.
- Discarded Clinical Samples: Researchers may also request discarded yet identified clinical samples from consenting participants and non-identifiable samples from participants who did not consent specifically to this or future studies. Discarded samples are those samples remaining after sampling and storage required for clinical evaluation and diagnosis. Typically these samples will be obtained from the CCHMC clinical laboratory. Samples are likely to include blood, urine, and/or bronchial lavage fluid. The samples will be used to determine allergen sensitization by specific IgE testing. Specific IgE and will be used in participants in whom skin-prick testing to common environmental and food allergens cannot be done or will be uninformative. The samples may also be evaluated for biomarkers of inflammation, oxidative stress or disease or used to obtain additional genetic material for genetic testing related to immune response, inflammation, oxidative stress or allergic or asthma related diseases.

- Saliva Samples: Saliva samples will be obtained by a trained professional during scheduled research or clinical visits and/or in the outpatient setting. Saliva will be collected in designated tubes or using specifically designed sponges in individuals who are not able to actively produce saliva upon request. Universal infection control precautions will be observed. All materials will be disposed of as dictated by CCHMC policy for hazardous waste. Nucleic acids and proteins will be removed from the cells collected, frozen and stored in a lab at CCHMC. For genetic testing related to immune response, inflammation, oxidative stress or allergic or asthma related diseases will be done on these samples. The results of the genetic testing of these and all the samples listed will be stored in a secure database.
- Trans-epidermal Water Loss (TEWL) Measurement and SCORAD: Participants may be evaluated for TEWL, which is the amount of water vapor that is lost through the skin as measured in grams/m2/hour. This measurement will be done non-invasively, using a specialized probe (diameter approximately equal to that of a one cent coin) which gently rests upon the skin for approximately 60 seconds for each measurement. Both affected and unaffected skin will be evaluated. The resulting data will be stored for future analyses. SCORing Atopic Dermatitis (SCORAD, a clinical tool used to assess the extent and severity of eczema) may also be performed.
- Nasal Epithelial Cells: Nasal epithelial (nose) cells will be obtained by placing a sterile brush a short distance into the subject's nose in order to remove cells from the lining of the turbinate. Nucleic acids and/or proteins may be removed from the cells and frozen. In some cases, nasal epithelial cells may be used to make immortalized or virus-transformed cell lines and frozen and stored in the laboratory for future evaluation of cellular responses, such as levels of interleukins and cytokines after addition of allergen. Expression analyses of RNA derived from primary nasal cells or cell lines and identification of viruses within the mucous may be performed. All samples will be stored in a lab at CCHMC. Testing for genetics related to immune response, inflammation, oxidative stress or allergic or asthma related diseases may also be performed on these samples.
- Urine dip for cotinine to evaluate SHS exposure. Participants and their parent/guardian will be asked to provide a urine sample in a specimen collection cup and a cotinine testing strip will be used to determine SHS exposure.
- Urine Pregnancy test – If the participant is a female who has started having periods, we will ask the participant to give us a small sample of urine for a pregnancy test. If the pregnancy test is positive, the participant is not eligible for the study. This information will be disclosed to the participant and parent. Sufficient urine for a pregnancy test must be obtained prior to enrollment of the participant in the study.
- Urine Metabolomic Analysis: Up to 50ml of urine will be collected in a sterile specimen cup and frozen as part of the GCPCR biorepository. Magnetic resonance spectroscopy (NMR) may be used to determine the differences in metabolomics profiles in urine samples. These profiles may be linked to immune

response, inflammation, or oxidative stress. The sample will be placed on ice until it is stored in a freezer.

- Fecal Microbiome sample: The participant and parent/guardian will be instructed on how to obtain a fecal microbiome sample. The sample will be collected by the family and stored in a specimen container in a ziplock bag and refrigerated until collection. The sample will be collected at V2, sent in by mail, or dropped off prior at CCHMC by parent/guardian or participant. This sample will be banked and stored in a freezer in the CCHMC Asthma Research Laboratory for future testing.
- Passive smoking cessation intervention: Parents/guardians or participants that are exposed to second-hand tobacco smoke by parental/guardian report will be offered a passive smoking cessation intervention. If participant or their parent/guardian identifies themselves as an active smoker, they will be offered a smoking cessation handout with community resources and a fax referral handout for the KY or OH 1-800 quit line.

Home Visit 1 (H1): This visit will be conducted by the study coordinators in the participant's home. During this visit, environmental samples will be taken and the family will be instructed on how to use the home trigger remediation equipment and educational materials.

Procedures done at these visits include:

- Asthma and Allergy related Questionnaires
- Download Propeller Health app on family's smartphone/iPad or provided iPad/Wi-Fi cradlepoint or give family a device that will allow Propeller to work (if the family doesn't have access to a smartphone or iPad with data plan).
- Give introduction to Propeller monitoring cap use and Propeller Health app. Participants will be encouraged to use only the inhalers with the caps on them and given instructions to call the study team for replacements if they lose or damage their inhaler caps. This may be done during their first clinic visit if the family has a device that works with Propeller.
- Assessment of Participant's home environment: Environmental data and housing characteristics (including but not limited to HVAC system design, presence of mold, water damage, etc.) will be collected by trained study personnel during a home walkthrough and recorded on the Home Walkthrough Checklist. This checklist collects information regarding dwelling characteristics, home cleaning practices, how the home is heated and cooled, visible mold and the use of humidifiers, dehumidifiers and air purifiers.
- Dust/air sampling: Household dust samples will be collected and banked at CCHMC. A dust sample will be taken from the child's bedroom and/or the child's primary activity room by the trained research coordinator. These samples will be collected into a filter fitted onto a vacuum hose. The carbon filters from the provided air purifier will be collected every 3 months and returned to the study staff for dust analysis. The dust samples may be analyzed for biomarkers of exposure or disease, including but not limited to allergen levels, air pollution, microbiome and mold. These factors will be included as potential predictors of disease development

and severity, and will also be analyzed in conjunction with biospecimen data (such

as serum cytokines and vitamin D levels, genetic polymorphism, gene expression and methylation levels, etc.) and personal and demographic characteristics.

- Dispense home trigger remediation package equipment and materials (dust mite mattress and pillow covers, cleaning supplies, HEPA filter and HEPA vacuum) & provide family with necessary training/education.

Propeller Health Inhaler monitoring and Web-based Platform

Propeller Health, a web-based inhaler cap monitoring sensor and mobile software management platform will be used to monitor how frequently the participant uses their inhaled asthma medication (Appendix B). The monitoring cap will be placed on both the controller and rescue inhalers by the study team at the first home visit (H1) and they will be registered with Propeller Health. The inhaler use will be recorded on the web platform. Starting the time of the initial self-management intervention session at month 3½, a mobile-based app program will be available for both android and IOS platforms and will allows the participant and family to interact directly with the platform. This is a FDA approved, HIPAA compliant device that has been demonstrated to improve asthma outcomes and adherence measures. This equipment has been approved by the CCHMC Equipment committee for use in prior studies. A contract and data use agreement was also approved for prior studies and will be reviewed and updated for the purposes of this study. Propeller Health may collect User PHI or PII and Usage Data from each user and generate de-identified data reports in accordance with the terms and conditions of the data use agreement signed by Propeller Health and CCHMC.

During the second month of the study, we will establish the participant's baseline adherence to daily asthma controller medication and need for rescue short-acting beta-agonist. Thus, the study team, participant and family will be blinded to this baseline data collection.

At the time of the initial self-management session month 3½, the Propeller Health platform will be turned on and data on the participant's baseline adherence to daily asthma controller medication and need for rescue short-acting beta-agonist shared with the study team, participant, and family. The participant and parent/guardian will receive the participant's inhaler usage for the current and preceding week. They will also receive smartphone alerts from the Propeller Health app reminding them to use their controller inhalers and alerts when they use rescue medication prompting them to select their symptoms and triggers based on a pre-populated list.

Propeller caps will be collected at the end of the study.

CCHMC Visit 2 (V2): The study coordinator will conduct this visit at CCHMC. The participant will complete asthma questionnaires, an Asthma Control Test (ACT), and the TreatSmart program on a CCHMC secured laptop. TreatSmart will determine if participant's treatment dose should remain the same or be changed based on their level of control. Asthma education will be reinforced. These procedures are similar to those outlined above in the baseline medical visit.

The study team will also review the results of the biomarker assays (genetic and environmental) and discuss the results with the family. One of the pulmonary or allergy specialist investigators (Guilbert, Durrani, Kercsmar, McDowell, Khurana Hershey,

pulmonary or allergy fellow or asthma research or pulmonary nurse practitioner) will perform a physical exam, review PFT report, review the TreatSmart program visit

summary and treatment recommendations, and make a personalized plan of medications and a revised home environmental trigger remediation plan based on the environment and genetic biomarker assays and self-management assessments. The visit summary, asthma medication and home trigger remediation plan recommendations and asthma action plan from the medical visit will be physically given to the participant and family. These documents in the form of a letter will be sent to the primary care provider by the study team.

For participants who will be getting a personalized self-management intervention, the study coordinator will also connect with one the CCHMC Adherence Health Psychology team investigators demonstrate a telehealth visit using CCHMC-provider Jabber Guest software (like Skype but HIPAA compliant) on a secure study smartphone to introduce them to the Adherence specialist. The smartphone-based Jabber Guest software has been implemented successfully in other clinical visits through the CCHMC Telehealth Program.

Prescriptions for asthma medications and inhaler spacers will be written by the study physician and offered to be sent to a delivery or routine pharmacy depending on the family's preference. The study coordinator will review how to take the medication with the participant.

Procedures done at these visits include:

- Asthma and Allergy related Questionnaires, ACT, TreatSmart
- Research clinic visit (CCHMC T building) with medical evaluation
- Pre-bronchodilator spirometry
    - Post-bronchodilator spirometry may be performed at the study physician's discretion
- Collection of fecal sample for fecal microbiome (if not already collected prior to visit) and urine pregnancy test: If the participant is a female who has started having periods, we will ask the participant to give us a small sample of urine for a pregnancy test. If the pregnancy test is positive, the participant is not eligible for the study. This information will be disclosed to the participant and parent.

Home Visit 2 (H2): This visit will be conducted by the study coordinators in the participant's home. During this visit, asthma and allergy related questionnaires will be completed and dust samples will be collected. If this is a participants final study visit, the study team will make sure that the participant has 2 additional refills at the end of the studyandthey will also be given a letter which summarizes which medication the participant was prescribed and the letter will encourage them to make an appointment and visit their primary care physician within 2 months of the study end. Information on how to make an appointment at CCHMC Asthma Center will also be provided.

Procedures done at these visits include:

- Asthma, allergy, and environmental related Questionnaires, ACT, TreatSmart
- Review personalized home trigger remediation plan with the family.
- Complete an assessment of the family's home by doing a walkthrough to assess for asthma/allergy triggers and to assess follow through of the personalized home trigger remediation plan
- Pick up Propeller monitoring caps (if applicable)

- Pick up iPad and cradlepoint (if applicable)
- Collect dust samples for environmental exposure assessment as described in H1.Collect HEPA filter and carbon filter from air purifier for dust analysis. Provide family with new HEPA filter and new carbon filter if needed.

CCHMC Visit 3 (V3)- Follow Up Medical Visit (Optional):

This additional visit will allow us to compare results of biological testing that we assessed during Clinic Visit 1 (pre-intervention) with post intervention biological testing to see if our studies intervention affected clinical values of the testing we reassessed between visits.

Participants will be asked to come in to CCHMC for this visit. If participants agree to participate in this portion of the study, they will be asked to sign an updated consent/assent form if applicable. If participants choose not to participate in clinic visit 3, they will be allowed to continue with the remainder of the study as per their initial signed consent/assent.

The study coordinators will conduct this visit. The participant will complete an Asthma Control Test (ACT), and the study coordinator will assist the participant in completing the TreatSmart program as described in visit 1. This program will produce a visit summary and asthma action plan. After the TreatSmart program is completed, one of the pulmonary or allergy specialist investigators (Guilbert, Durrani, Kercsmar, McDowell, Khurana Hershey), pulmonary or allergy fellows, or asthma research or pulmonary nurse practitioner will perform a physical exam, review PFT report, review the TreatSmart program visit summary and treatment recommendations, and make a final decision of the level of asthma control and asthma medication needed. The asthma action plan and any medication recommendations from the medical visit will be physically given to the participant and family. These documents, in the form of a letter, will be sent to the child's primary care provider by the study team.

Prescriptions for asthma medications and inhaler spacers will be written by the study physician and offered to be sent to a home delivery or routine pharmacy depending on the family's preference. The study coordinator will also provide basic asthma education to the participant if needed.

Procedures done at these visits include:

• Sign updated consent/assent, complete Asthma, Allergy and study related Questionnaires, ACT, and Treat Smart Research clinic visit with medical evaluation

Biological Samples and Measurements:

- Pulmonary Function Testing (PFT) / Spirometry: Children may be asked to undergo PFT. PFTs will be conducted according to ATS criteria by personnel who have completed a spirometry training course. A spirometer will be used that meets ATS standards. Some asthma medicines will be stopped from 8 to 24 hours before the PFTs to meet ATS standards. The participants and their families will be instructed on which medicines not to take before the test and informed that stopping asthma medicines may make their asthma symptoms worse. They will also be instructed that if the child has asthma symptoms, they should NOT stop taking their medicine, and we will reschedule the test. If the child starts to have asthma symptoms after stopping the medicine, we will recommend that the child resume the medicines as

prescribed. Nose clips and disposable bacterial/viral mouthpieces will be used. The children will be coached through each standard forced expiratory maneuver in a seated position. A post-bronchodilator test will be obtained. The children may be given up to 6 puffs of albuterol and lung function may be repeated to look for reversibility per ATS guidelines. The most common risks associated with albuterol use is a high heart rate or lightheadedness.

- Skin Prick Allergy Testing: Skin prick allergy testing on the participants' forearm or back by a trained professional may be performed on participants. The test will include the following antigens: dust mite, cat, dog, cockroach, mold mixes (2), ragweed, grass mixes (2), tree mixes (2) and foods. Participants having allergy skin prick testing. The results of these tests will be mailed to the parent/guardian and participant after the visit to share with their primary care physician. The results will be used to indicate allergen sensitization. Because antihistamines will interfere with the skin testing, the parents/guardian may be asked to refrain from

giving the child any antihistamines in the week before their visit. If the child requires antihistamines in the week before the study visit, the visit will be rescheduled.

- Blood: The amount of blood drawn may not exceed 50 ml or 3 ml per kg whichever is lesser, and collection will not occur more frequently than 2 times per week. Participants will be asked if they have had any blood drawn or plan to have any blood drawn within the 24-hour period of the research draw. Blood will be collected by study coordinators or by trained phlebotomists at the CCHMC Test Referral Center or the Schubert Research Clinic, provided that this amount is safe for the participant. If the age or condition of the patient limits the amount of blood that can be collected, this may be omitted or a smaller amount may be collected that is more appropriate. A numbing agent may be used to decrease the pain associated with venipuncture if requested by the parent/guardian. Blood may be used to isolate nucleic acid or proteins using standard protocols. Whole blood, serum, plasma or other blood components like peripheral blood mononuclear cells (PBMCs) may be obtained from the blood by the CTRC Laboratory, the CCHMC Clinical Laboratory, or an investigators' laboratory and either used immediately or stored for future studies. The blood samples may be sent to Stanford University for analysis by mass cytometry. Blood may be evaluated for biomarkers of inflammation, oxidative stress or disease, vitamin D, complete blood count and differential, and/or specific IgE and total IgE using standard techniques. In some cases, blood may be used to make immortalized or virus-transformed cell lines and frozen and stored in the laboratory. Blood components or cells lines may be used to identify immunological and environmental markers of exposure or allergic disease including, but not limited to evaluation of cellular responses, interleukins, cytokines, fluorescent plasma oxidative stress products. Genetic testing related to immune response, inflammation, oxidative stress, allergic, environmental exposures, or asthma related diseases may also be performed. The results of the vitamin D level, IgE and complete blood count and differential will be reviewed by one the study physicians. If abnormal and felt to be clinically relevant, it may be repeated at the physician's discretion.
- Discarded Clinical Samples: Researchers may also request discarded yet identified clinical samples from consenting participants and non-identifiable samples from participants who did not consent specifically to this or future studies. Discarded samples are those samples remaining after sampling and storage required for clinical evaluation and diagnosis. Typically these samples will be obtained from the CCHMC clinical laboratory. Samples are likely to include blood, urine, and/or bronchial lavage fluid. The samples will be used to determine allergen sensitization by specific IgE testing. Specific IgE and will be used in participants in whom skin-prick testing to common environmental and food allergens cannot be done or will be uninformative. The samples may also be evaluated for biomarkers of inflammation, oxidative stress or disease or used to obtain additional genetic material for genetic testing related to immune response, inflammation, oxidative stress or allergic or asthma related diseases.

- Saliva Samples: Saliva samples may be obtained by a trained professional during scheduled research or clinical visits and/or in the outpatient setting. Saliva will be collected in designated tubes or using specifically designed sponges in individuals who are not able to actively produce saliva upon request. Universal infection control precautions will be observed. All materials will be disposed of as dictated by CCHMC policy for hazardous waste. Nucleic acids and proteins will be removed from the cells collected, frozen and stored in a lab at CCHMC. For genetic testing related to immune response, inflammation, oxidative stress or allergic or asthma related diseases will be done on these samples. The results of the genetic testing of these and all the samples listed will be stored in a secure database.
- Trans-epidermal Water Loss (TEWL) Measurement and SCORAD: Participants may be evaluated for TEWL, which is the amount of water vapor that is lost through the skin as measured in grams/m2/hour. This measurement will be done non-invasively, using a specialized probe (diameter approximately equal to that of a one cent coin) which gently rests upon the skin for approximately 60 seconds for each measurement. Both affected and unaffected skin will be evaluated. The resulting data will be stored for future analyses. SCORing Atopic Dermatitis (SCORAD, a clinical tool used to assess the extent and severity of eczema) may also be performed.
- Nasal Epithelial Cells: Nasal epithelial (nose) cells may be obtained by placing a sterile brush a short distance into the subject's nose in order to remove cells from the lining of the turbinate. Nucleic acids and/or proteins may be removed from the cells and frozen. In some cases, nasal epithelial cells may be used to make immortalized or virus-transformed cell lines and frozen and stored in the laboratory for future evaluation of cellular responses, such as levels of interleukins and cytokines after addition of allergen. Expression analyses of RNA derived from primary nasal cells or cell lines and identification of viruses within the mucous may be performed. All samples will be stored in a lab at CCHMC. Testing for genetics related to immune response, inflammation, oxidative stress or allergic or asthma related diseases may also be performed on these samples.
- Urine dip for cotinine to evaluate SHS exposure. Participants and their parent/guardian may be asked to provide a urine sample in a specimen collection cup and a cotinine testing strip will be used to determine SHS exposure.
- Urine Pregnancy test – If the participant is a female who has started having periods, we will ask the participant to give us a small sample of urine for a pregnancy test. If the pregnancy test is positive, the participant is not eligible for the study. This information will be disclosed to the participant and parent. Sufficient urine for a pregnancy test must be obtained prior to enrollment of the participant in the study.
- Urine Metabolomic Analysis: Up to 50ml of urine may be collected in a sterile specimen cup and frozen as part of the GCPCR biorepository. Magnetic resonance spectroscopy (NMR) may be used to determine the differences in metabolomics profiles in urine samples. These profiles may be linked to immune

response, inflammation, or oxidative stress. The sample will be placed on ice until it is stored in a freezer.

- Fecal Microbiome sample: The participant and parent/guardian may be instructed on how to obtain a fecal microbiome sample. The sample will be collected by the family and stored in a specimen container in a ziplock bag and refrigerated until collection. The sample will be collected at V3, sent by mail, or dropped off at CCHMC by parent/guardian or participant. This sample will be banked and stored in a freezer in the CCHMC Asthma Research Laboratory for future testing.
- Passive smoking cessation intervention: Parents/guardians or participants that are exposed to second-hand tobacco smoke by parental/guardian report may be offered a passive smoking cessation intervention. If participant or their parent/guardian identifies themselves as an active smoker, they will be offered a smoking cessation handout with community resources and a fax referral handout for the KY or OH 1-800 quit line.

If this visit is the participants final study visit, the study team will make sure that the participant has 2 additional refills at the end of the study. They will also be given a letter which summarizes which medication(s) the participant was prescribed, and the letter will encourage them to make an appointment and visit their primary care physician within 2 months of the study end. Information on how to make an appointment at CCHMC Asthma Center will also be provided.

Self-Management Intervention: These visits will occur via the family's smartphone or iPad (or study provided iPad or device in the case that the family does not have a smartphone available) in the participant's home starting at month 3½. For participants with ≤50% adherence during the first two months of the study will have self- management visits occur every 2 weeks (total of 4), and one booster session, with the goal to improve inhaler adherence. One of the CCHMC Adherence Health Psychology team specialists will connect for a self-management telehealth visit using CCHMC-provider Jabber Guest software. The smartphone or iPad based Jabber Guest software has been implemented successfully in other clinical visits through the CCHMC Telehealth Program. Parent/guardian participation is required for these visits for children < 11 years. In the event that Jabber is not working during the self-management sessions or other issues arise, the session may be completed by phone call or by Skype if necessary.

Self-management visits may be audio-recorded for fidelity checks. These recordings will be de-identified and password-protected. Audio-recorded treatment sessions are used for the purpose of verifying that treatment protocols are followed.

Adherence data from the Propeller Health monitoring system will be available to families beginning at the time of the initial self-management visit via the Propeller app. This data will also be reviewed with the participant by the adherence specialist during adherence visits and one of the study staff during the second medical visit. The adherence specialist will also provide customized supportive text messages originating from the CCHMC email system to the participant's smartphone or iPad. Text messages will not include personal health information, but instead will provide support and reminders related to adherence (e.g., Hello, remember to use your inhaler today!, Don't forget to put a reminder in your locker, Have you been using your monitoring log?).

Participants with 51-79% adherence rates during the first two months will receive a text messaging only intervention, with text messages being sent from the CCHMC email system to the participant's smart phone or iPad to aid with adherence, problem-solving and motivation. Similar to the previously mentioned intervention, text messages will provide support and reminders related to adherence (e.g., Hello, remember to use your inhaler today!, Don't forget to put a reminder in your locker, Have you been using your monitoring log?).

Participants with ≥ 80% adherence rates during the first two months will not receive any adherence intervention.

Phone Calls: Up to ten scheduled phone calls will be made during the study to the family smartphone or home telephone to complete the Asthma Control Test, the Treatsmart program, and the concomitant medication form to document any changes to medications since the last phone call or study visit. These phone calls will collect our primary outcomes after the intervention is delivered and also serve as a point of contact to keep the families engaged in the study. During the call, the family will be asked to upload their data from the Propeller Adherence app from their smartphone or iPad. One of the pulmonary or allergy specialist investigators (Guilbert, Durrani, Kercsmar, McDowell, Khurana Hershey) will review the TreatSmart program data summary, any new medications that were started, and treatment recommendations. If a medication change is needed, a sick visit will be scheduled with a study investigator at one of their upcoming clinics. If a monthly phone call is missed or unable to be completed during a monthly phone call visit window, an

“unscheduled” phone call may be completed in order to maintain contact with the family at any point during the study.

Sick Visit: The study physician will perform a medical exam and determine the level of asthma control and if asthma medication adjustment is needed. The visit summary, asthma medication recommendation and asthma action plan from the sick visit will be physically given to the participant and family. These documents in a form of a letter will be sent to the school nurse (if the school nurse referred participant to the study) and primary care provider by the study team.

Prescriptions for asthma medications and inhaler spacers will be written by the study physician and offered to be sent to a home delivery or routine pharmacy depending on the family's preference. The study coordinator will review how to take the medication with the participant.

Unscheduled/Unplanned Visit:
An unscheduled/unplanned visit may need to occur if one or more planned procedures were not completed, or a result was not obtained. Any of the assessments listed under section 8 (Study Procedures) may be conducted either for the first time or for reassessment. No participant will be subjected to an assessment for which he or she has not provided written consent or assent, and no informed consent/assent form will contain any information that has not been approved by the IRB.

The unscheduled/unplanned visit will be scheduled to occur at CCHMC (T Clinic).
The participant will be compensated $25 for their time and effort.

Follow Up/Repeat Home Visits:
A follow up home visit may need to occur after H1 if any of the home visit procedures/tasks were not able to be performed or completed. A repeat home visit may need to occur if a family moves during the study. All procedures done during H1 may be repeated in their new home if needed, as well as help with setting up home remediation supplies provided during H1.

Asthma Exacerbations during Study Follow-up:
The participant's asthma action plan contains advice for handling increased or severe asthma exacerbations and when to call the study team or when the family should take the child for evaluation to the school nurse, school-based health clinic, community primary care provider, or a local urgent care or emergency department. This data will be collected at the patients next study visit if the family didn't call the study team. The school nurse (if the school nurse referred participant to the study) or PCP will also be encouraged to contact the study team if additional advice on the asthma treatment of a study participant is desired. The study team can then determine if a sick visit is needed.

In addition, the CCHMC study team will receive a Propeller Health a weekly report of participants that have not taken their daily controller medication in the last 7 days, have changed their asthma symptoms control level, or have experienced a 200% increase in their rescue medication use in the past 24 hrs. The study team will communicate with the participant's family to gather more information on the severity of their asthma symptoms using the Phone Call Exacerbation Form. If the participant is experiencing severe symptoms, they will be encouraged to be urgently evaluated by the school nurse, school-based health clinic, community primary care provider, or a local urgent care or emergency department.

Other:
Community Engagement: A goal of this initiative is to identify as many DTT patients as possible from community sites. We will accomplish this by capitalizing on our existing partnership with CPS and CHD by providing them an enhanced tool for the school ACT screening program. This program currently screens over 80% of the asthmatics attending CPS schools; we will offer the screening tool to FQHC and CHD practices as well. The identified patients will be invited to participate and all will be

identified to school nurses and their PCMHs. For those who choose not to participate in the program, we will collect reason for non-participation, share it with our community

partners, and use the data to improve our program and identify alternative interventions for non-participants. Referral to existing programs, a CCHMC specialty asthma clinic, or a school-based health clinic will be offered. In addition, we will provide clinical support via telephone or telemedicine consultation for the school nurses,

School-based health clinic personnel and primary care providers who may have questions or concerns about the DTT patients. Similar resources will be made available for enrolled patients as well. We will conduct meetings with community partners through the CCTST community partner council and Children's Health Initiative Committee to involve community partners in design, enhance community awareness and patient engagement. We will also connect the child's school nurse and primary care physician by sending summary of visits, in-depth risk profile, and recommended personalized treatment plan for all enrolled children.

Dissemination plan.
One of the objectives for the study is to engage 3 target stakeholder communities in our study: 1) CCHMC clinical providers; 2) community pediatric clinical providers (within schools, community clinics, community centers, etc.), and 3) study participants and their caregivers. Engaging participants will be particularly important for retention of subjects over the follow-up period. To this end, we plan to produce similar but tailored quarterly newsletters for each target population. In addition, our study participants will receive a welcome or orientation newsletter. The goal of the newsletters are to: 1) inform stakeholders about the purpose/objectives of the study and/or provide study progress updates; 2) highlight the stories of participants and their caregivers (with their permission); 3) disseminate summary study findings and related learnings; and 4) offer other educational and other research opportunities. Newsletters will be produced electronically (i.e. Mail Chip) and emailed or texted to stakeholders. PDF versions can also be printed and mailed via the US Postal Service. Newsletters may include links – for example, to entertaining and/or informative videos, short/fun quizzes and/or games. All materials will be submitted for IRB review prior to use. The newsletter may also be posted on a CCHMC external website. All clinical providers will also be emailed the newsletter.

Study Termination. During each medical visit, the number of severe asthma exacerbations [treated with systemic steroids; hospitalizations for asthma; PICU admission, intubation or hypoxic seizure due to asthma] since the start of the study will be determined. If the participant has $\geq$ 4 severe asthma exacerbations or > 2 asthma-related hospitalizations during the study, study participation will be ended. The procedures for the end of study will also be followed with the recommendation of referral to the CCHMC Difficult-to-Treat Asthma Clinic.

If patient/patient's family are not able to be reached for multiple weeks throughout the study, a MOP has been put into place as a plan for re-gaining communication. Please refer to the *Study Discontinuation MOP* for more details regarding this communication plan. If plan has been carried out and study staff are still unable to reach patient/patient's family, the participant will be discontinued from the study. In the event that a participant is discontinued from the study, a letter will be mailed to the patient/patient's family with instructions to resume asthma care from the physician who was treating them prior to the study.

If a participant was loaned a device, an iPad or Cradlepoint to complete the Telehealth portion of this study, these devices will be collected upon study termination/completion. If

a participant completes all study activities, this equipment will be collected at the final home visit (H2) or once the self-management visits are completed coordinators will schedule to come pick up the equipment from the family's home. If a participant is discontinued from the study early due to lost to follow-up, study staff will follow the *Study Discontinuation MOP* in order to collect the loaned iPad and Cradlepoint. The actions taken will include: phone calls, text messages, emails, letters mailed to the home, and home visits. If the equipment is not recovered, a certified letter will be sent to the home with instructions to return the iPad and Cradlepoint with a copy of the *Telehealth Agreement Form* that was signed at the first Home Visit (H1). Per the signed *Telehealth Agreement Form*, families are responsible for notifying CCHMC if the iPad is lost or stolen. "iPad's that are lost or stolen will be reported to the CCHMC Protective Services Department and to the appropriate Police Department". If the equipment is not returned after all steps in the *Study Discontinuation MOP* have been followed, the Telehealth department at CCHMC will be notified that the equipment was not recovered.

9. DATA ANALYSIS/METHODS:

Study Outcomes:

The adolescent's asthma outcomes and adherence will be measured at baseline and during the clinical visits or study telephone calls once a month for a total of 12 months. Outcomes will be measured during the monthly medical visits using a computerized TreatSmart program based on the NAEPP asthma guidelines which was adapted by the CCHMC Asthma Center database team from the Inner City Asthma Coalition (Appendix C), ACT scores, and Propeller Health web-based inhaler cap monitoring sensor and mobile software management platform (Appendix B).

Primary Outcome:
Composite asthma severity index (CASI) score collected monthly during phone calls, home visits, and clinic visits over 1 year. The CASI is a severity score of symptom burden, exacerbations, healthcare utilization, lung function and dose of inhaled corticosteroids. This score will be collected and captured by the TreatSmart program.

Secondary Outcomes:
We will analyze the following outcomes: ACT score over past 4 weeks; rescue medication use, oral-steroid requiring exacerbations; healthcare utilization, lung function, dose of inhaled corticosteroids, and adherence of controller medication.

These asthma related outcomes are commonly reported in both the adult and pediatric asthma literature and are endorsed by national asthma guidelines and the National Institutes of Health (NIH) asthma-outcome conference.

Data Analysis
We will use descriptive statistics to characterize the sample demographics. A descriptive analysis with calculation of means, medians, and standard deviations will be performed for each continuous measure; categorical measures will be examined with percentages. If necessary, we will log-transform non-normal data; however if a normal distribution cannot be attained we will use nonparametric statistics. We will use paired t-tests to evaluate the null hypothesis that there was no change in the primary outcome (CASI score) while participants are blinded to data collected by the Propeller medication sensor in the first month of participation. Nonparametric methods will be used if the assumptions for paired t-tests are violated. The primary analyses will test whether this interventional program improves CASI scores (from completion of the first month to study exit). Linear mixed effects models with a random effect for subject assessed changes in primary asthma endpoints each month across the 1 year study or upon exit. Participants with one or more observations will be included in the analysis. All statistical analyses will be implemented in SAS 9.3 (SAS Institute, Cary, NC) and use a significance level of 0.05. Potential confounders identified from the literature, such as age, gender, season of enrollment, severity of asthma at baseline, smoke exposure, environmental exposures and atopic status will be adjusted in the analyses. The REML model used for these analyses requires that any missing data are “missing at random” (MAR) to yield valid estimates. To account for the presence of possible non-ignorable missing data, pattern- mixture modeling will be applied for these analyses.

The secondary analyses will look at the ACT score, rescue medication use, oral-steroid requiring exacerbations, healthcare utilization, lung function, dose of inhaled corticosteroids, and adherence of controller medication. Linear mixed-effect models will be used to compare the continuous outcomes such as exacerbations. Generalized linear mixed effect models will be used to compare the discrete outcomes such as health system utilization, both accounting for repeated measurement over time while adjusting for confounders.

These results will be used to inform cluster analysis to determine the combinations of biomarkers and that are most predictive of the CASI scores and clinical outcomes.

Future use

The de-identified data may be used for future research, analysis or recruitment. Audio recordings from the self-management visits will be will be destroyed following completion of the study. All re-identification codes will be destroyed.

10. FACILITIES and PERFORMANCE SITES:
The Cincinnati Children's Hospital and Medical Center CCHMC Pulmonary and Asthma Research Divisions, and CTRC.

11. POTENTIAL BENEFITS:
Participants will have direct benefit of being closely monitored for their asthma and clinical care. The future benefit is to determine if a personalized plan of medications and home environmental trigger remediation plan based on environmental evaluation, all biomarker assays and self-management assessments can improve asthma outcomes in neighborhoods where the incidence of asthma is especially high.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:
The risks to participants are minimal and include:

- **Questionnaires**: Asthma, Allergy, environmental, depression, anxiety, and dietary intake questionnaires will be collected. There is a slight inconvenience to the family in the time required to answer questionnaires. There are no risks associated with completing study questionnaires. All data will be entered into a secure database, password protected, and only authorized study staff will have access. The participant will not be required to answer any questions on the questionnaires that they decline a response. The PROMIS depression questionnaire is a research tool that assesses symptoms of depression without the use of critical items (e.g., suicidality) that may be associated with increasing the liability to the investigative team or institution. Although the PROMIS depression questionnaire is a primarily used as a research tool, a score of 70 or higher is correlated with depression. If a score of 70 or higher is obtained on the child's questionnaire, the CRC will inform the study physician and the study health psychologist. The study physician will let the family know the questionnaire result and that it suggests that their child may have depression but this would need to be confirmed by a mental health professional who will be contacting them within 24 hours. A study psychologist or psychology fellow will follow up with patient in 24 hours. Study personnel will also give the family a mental health and behavior resource handout that the study psychologist may use. If the participant or parent answer yes to question #15 on the food assessment questionnaire, they will be given a food resource handout.
- The spirometry has an extremely small risk of causing dizziness. If participants experience dizziness, children will be asked to remain seated 5 minutes before continuing.
- The risks associated with skin prick testing are minimal and may include slight discomfort associated with the application of environmental prick tests and pruritus at the site of the pricks of positive reactions. Patient discomfort will be attempted to be minimized by the use of a fan to blow on the site of the skin pricks. There is no risk of systemic reactions to prick tests in individuals without a history of allergy (4,5). A medical provider trained in treating anaphylaxis will be available to provide

immediate treatment in the rare event that a participant experiences systemic allergic reaction. A study clinician may provide a topical corticosteroid or oral antihistamine to treat these symptoms. Stopping antihistamines before skin testing may make allergy (but not asthma) symptoms worse. Parents will be asked to stop their child's antihistamine usage 5 days prior to a study visit. They will also be told their child can chose to take their antihistamines if they need them, but the skin prick test will need to be rescheduled.

- Risks associated with phlebotomy include a slight hematoma at the sight of venipuncture. Therisks will be minimized by: (1) the use of trained personnel who will be drawing the blood using a small gauge needle and applying pressure to the site after withdrawal of the needle; and (2) individuals with any history of a bleeding diathesis will be excluded. (3) a numbing agent may also be used with young children to help to numb the vein from which the blood is drawn.
- The risks associated with obtaining a nasal scraping from the inferior turbinate include some temporary discomfort during the procedure (which lasts less than 30 seconds), as well as slight bleeding and/or bruising that may develop at the sight of scraping. The risks will be minimized by: (1) the use of trained personnel who are experienced in obtaining nasal epithelium biopsies; and (2) the exclusion of individuals with any history of a severe bleeding diathesis.
- There are no known risks for the pregnancy test. If the participant is under the age of 18, the results of the pregnancy test done for this study will be given to the parents/guardian.
- The collection of saliva, trans-epidermal water loss, stool and urine for metabolomics pose no risk.

Concerns about Accessing Adult Websites and Apps on CCHMC provided iPads:

- Participants will be provided with an iPad and cradlepoint for internet access in their home during the study if they do not have access to a smart phone or iPad with a data plan. This is similar to the equipment and system used in the CCHMC general pediatric clinics for sick calls, and the equipment will be provided by the CCHMC Telehealth Center. If it is determined that a participant requires an iPad and/or cradlepoint, participants will be asked to use the provided iPad "as they normally would use any device that has internet access". The family will be asked to sign a consent for the use of the iPad/cradlepoint modeled from that used by CCHMC general pediatrics. The iPad will have the Jabber and Propeller app pre-installed, and cannot be used to access the internet or use other apps. This equipment will be returned at end of study during the H2 visit. If this equipment is needed, a consent form for this equipment will be discussed with and signed by the parent/guardian at the H1 visit.
- The iPads will be loaded with a security software program Air Watch. Parent/guardian and participants will then be given an instruction sheet on how to use the iPad. CCHMC IT will be alerted if the Propeller Health app or Jabber app is removed from the iPad. The Air Watch security software enforces specific security measures, such as passcode and encryption. The study team working

with the CCHMC IT department will be able to erase all content in the event of a lost/stolen device. The Air Watch security software does not monitor the participants' usage or personal information. Internet access on the iPad is being restricted with Apple's built in Adult Content Filter for the Safari web browser. This content filter does its best to block websites with inappropriate content. The Internet content filter can identify, with a high degree of accuracy, whether a Web page is safe or not by examining various properties of the website including text and structure. The content filter is being managed by the Air Watch security software and cannot be removed.

13. RISK/BENEFIT ANALYSIS:
This study is minimal risk with direct benefit to the participants. It provides more comprehensive asthma management and monitoring than many of these participants currently receive.

14. DATA SAFETY & MONITORING (DSMP):
The Data Safety and Monitoring Plan (DSMP) will consist of a Steering Committee made up of key study personnel. The committee will meet a minimum of annually to review adverse events and to provide oversight and coordination of project management, research administration, publications and data sharing, and integration of all resources needed for the project.

Adverse Events:
Events that are unexpected and related to the conduct of any study-related visits will be reported promptly to the IRB according to IRB policy. Serious, life threatening events that are related to study related procedures will be reported to the IRB within 48 business hours. All other adverse events that happen in the course of study procedures as well as minor deviations from protocol will be reported in table form at the next continuing review.

For this study, the occurrence of wheezing or asthma exacerbations, and the development of allergic rhinitis are anticipated events and will be recorded as expected AEs. This information will also be collected on other study forms. Fluctuations in the status of pre-existing atopic dermatitis, a process that is expected to wax and wane in severity, will not be recorded as an AE unless, in the opinion of the site investigator, the degree of deterioration is unexpected for the participant. An abnormal complete blood count and differential, IgE or vitamin D level that is persistently abnormal once repeated, felt to be clinically relevant by a study physician, and requires referral to a specialist will be considered an adverse event.

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed or is not consistent with the risk information described in the general investigational plan.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes (21 CFR 312.32(a)):
1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Wheezing episodes and exacerbations of asthma are anticipated events in the population under study even when receiving standard of care therapy. A hospitalization for wheezing or asthma will not be recorded as an SAE unless it is considered a serious and unexpected suspected adverse reaction SUSAR (9.3.2). All other hospitalizations will be recorded in the case reporting forms.

Review with family of possible adverse events will be done at study visits and follow-up phone calls by the research coordinator if adverse events occur, will be documented. Adverse events will be recorded on an Adverse Event Reporting Form and will be reviewed at the meeting of the Steering committee.

If a parent/guardian response or complaint is not an expected adverse event (see section 4) or if the adverse event presents with greater than expected severity, the adverse event will be brought to the Investigator's attention in a timely manner for evaluation. The reviewing investigator will determine if the event is a Reportable Event as defined below.

Definition of Reportable Events
Reportable events must fall into one of the categories below:

1. Adverse event that is BOTH unexpected AND related or possibly related to participation in the research. This is regardless of whether internal or external site or seriousness.
2. An event that requires a change to the protocol or informed consent.
3. Information that indicates a change to the risks or potential benefits of the research.
4. Breach of confidentiality.
5. Change in labeling or withdrawal from marketing for safety reasons of a device used in research protocol.
6. Change to protocol made without prior IRB review to eliminate an apparent immediate hazard to a research participant.
7. Protocol violation that harmed a participant or others or indicates that participants or others are at increased risk of harm.
8. Incarceration of a participant in a protocol not approved to enroll prisoners.
9. Complaint of a participant that indicates unexpected risks or cannot be resolved by the research team.
10. Other unanticipated problem posing potential risk to participants or others comparable to the events listed above that are BOTH unexpected/unanticipated AND have a reasonable possibility of relatedness to the research.
11. INVESTIGATIONAL DEVICES: Unanticipated adverse device effect, deviation from the protocol to protect the life of a subject in an emergency, or any use of the without obtaining informed consent.

15. PRIVACY and CONFIDENTIALITY:
Confidentiality of Participant Data:
Precautions to protect the privacy of participant data include:

- Participants will be given a study ID that does not include any personal identifiers for study records and questionnaire data stored outside of CCHMC EPIC.
- A study ID not related to any PHI will be used in the study database.
- All electronic research data will be reviewed by the statisticians without PHI.
- The ID code and the research records will be maintained in a secured location and/or in password protected databases.
- Summary of the medical and adherence visits will be documented in the CCHMC EPIC medical record which can be accessed by school nurses (if the school nurses referred a participant to the study) and community primary care physicians who have been granted read-only access by CCHMC.
- Propeller Health data is stored on a HIPPA compliant server and has been approved by CCHMC IT and equipment committee.
- TreatSmart program and data are located on a CCHMC secure server.

To minimize risk, the source documents and audio recordings of self-management visits will be kept in the research record and stored in a secure location. Data will be entered into password protected databases with participants identified with a study number that contains no PHI. To minimize the inconvenience, we are limiting administration of the baseline questionnaires to the baseline visit. The adherence questionnaire will be given at the first and last medical visit. The TreatSmart program will take 10 minutes to complete.

We will also ask the parent permission for the research staff may contact them in the future to invite them to participate in future studies.

16. COST OF PARTICIPATION:
There is no cost to participants for the Propeller caps, medical care, self-management skill training or home environmental visits and remediation equipment and materials received as part of the study visits.

The cost of prescriptions and sick visits will be the responsibility of the subject and their insurance.

17. PAYMENT FOR PARTICIPATION:
This compensation is for reimbursement of time for the parent/guardian and participants for time spent in visit and as an honorarium for their ongoing participation.

All compensation given to participants will be in the form of ClinCard. A ClinCard is a reloadable debit card. Incentives will be loaded onto the card after each visit according to the payment schedule. Participants will receive a handout to explain the use of the card. Participants will receive a graduated amount to facilitate retention.

V1: $100 added to their ClinCard and the child will be offered small toys from a treasure chest (value <$3).

V2: $75 added to their ClinCard and the child will be offered small toys from a treasure chest (value <$3).

V3: $100 added to their ClinCard and the child will be offered small toys from a treasure chest (value <$3) (optional visit).
H1: Home trigger remediation gift package: HEPA vacuum (value $55); dust mite mattress cover ($29); two allergen proof pillow cover ($10); HEPA filter ($149); Cleaning supplies ($20).
H2: $75 added to ClinCard
Telehealth self-management visits and 10 monthly calls: $10 added to their ClinCard for each of 10 scheduled phone calls completed with parent/guardian and up to 5 self-management telehealth sessions.
Optional Stool Collection: $25 added to ClinCard (once sample is received)

For a total up to $525 added to ClinCard, as well as an asthma gift package for the home valued at approximately $255.

18. References

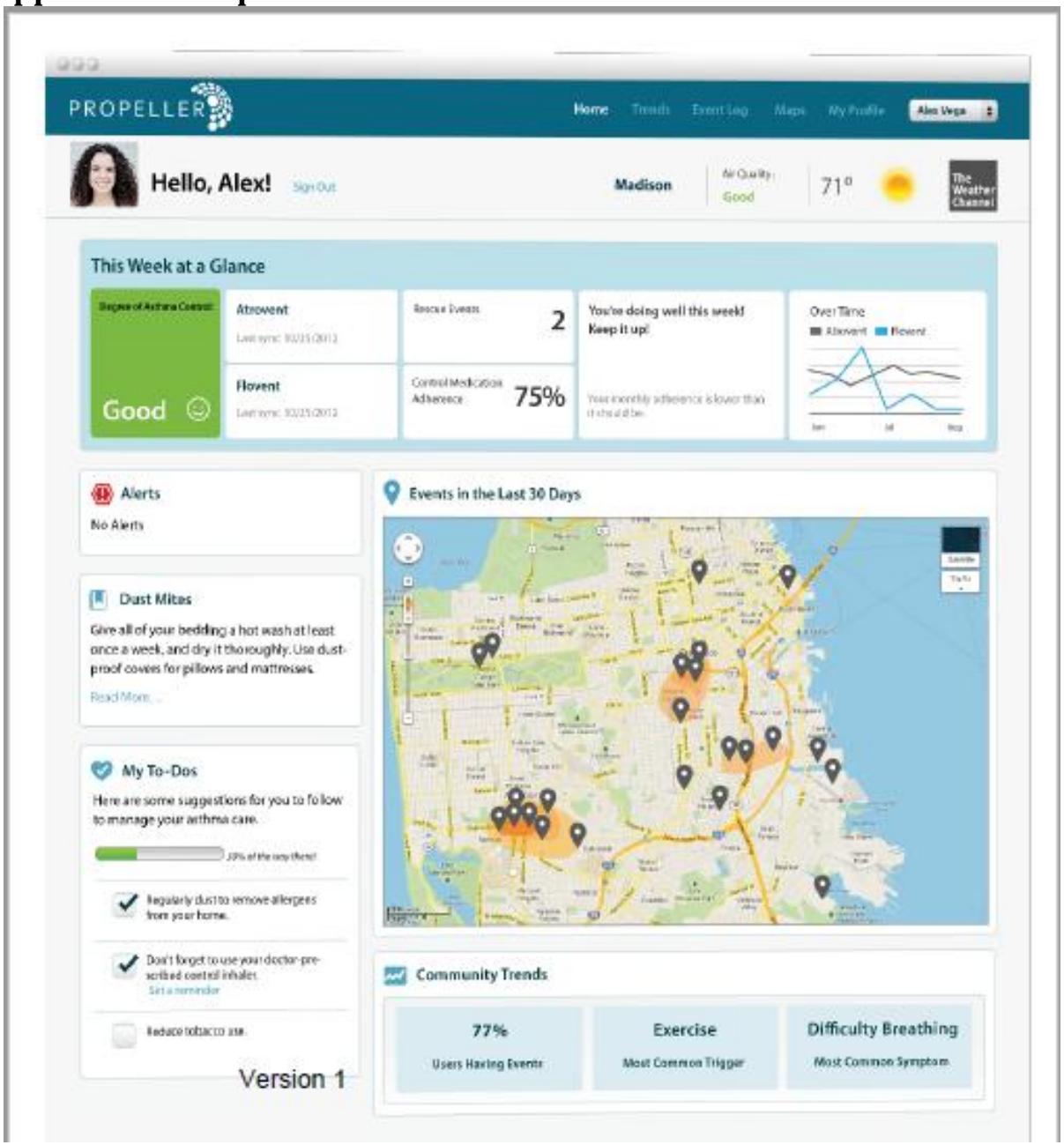
1. Wildfire JJ, Gergen PJ, Sorkness CA, et al. Development and validation of the Composite Asthma Severity Index—an outcome measure for use in children and adolescents. J Allergy Clin Immunol 2012;129(3):694-701.
2. Dexheimer JW, Gu L, Kercsmar C. Design of the asthma treat smart system in a pediatric institution. Stud Health Technol Inform. 2013;192:1004.
3. Merchant RK, Inamdar R, Quade RC. Effectiveness of Population Health Management Using the Propeller Health Asthma Platform: A Randomized Clinical Trial. J Allergy Clin Immunol Pract. 2016;4(3):455-63.
4. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113(1):59-65.

Appendix A: Study Procedures

Visit Type	**V1**	**H1**	**P1**	**P2**	**V2**	**SM1**	**SM2**	**P3**	**SM3**	**SM4**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**H2**	**SMB/ V3 (optional)**
Time (Visit windows: +/- 6 weeks for V2; +/- 16 weeks for V3; +/- 4 weeks for H, P and SM visits)	Day 1	Week 1	Month 1	Month 2	Month 31/2	Month 3 1/2	Month 4	Month 4	Month 4 1/2	Month 5	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	Month 12
Procedures																			
History & Physical	X				X														X
Questionnaires	X				X														X
Asthma Ed Handouts	X				X														X
Asthma TreatSmart-CASI (web based)	X	X	X	X	X			X			X	X	X	X	X	X	X	X	X
Telehealth Introduction to Adherence Staff	X																		
Allergy skin prick testing	X																		
Blood draw for biomarkers	X																		X
Nasal sample	X																		X
Pre- & Post-Bronchodilator Spirometry	X				X														X
Prescriptions as needed	X				X														X
Load Propeller Health app on family's smart phone	X	X (if not done at V1)																	
Telehealth Self Management Visit						X	X		X	X									
Review Propeller Health cap use		X																	
Download Propeller Health Inhaler Adherence Data			X	X	X	X		X	X		X	X	X	X	X	X	X	X	X
Environmental Risk Questionnaire		X																	
Collection of home environmental samples		X																X	
Dispense & training of family on home trigger remediation equipment & materials		X																X	
Dispense propeller data cap		X																	
Personalized Plan based On environment, biomarkers, self-management assessments					X (plan update)														
Pick up/Collect caps																		X	X

SM=Telehealth Self-Management Visit
H=Home environmental visit
P=Phone call
V=CCHMC T1 research clinic visit
*add-on sick visits as needed

Appendix B: Propeller Screen Shots



Appendix C: Treatsmart Medications