

Asthma Express: Bridging the Emergency to Primary Care in Underserved Children
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Asthma Express: Bridging the Emergency to Primary Care in Underserve Children

PI: Dr. Arlene Butz

1. SPECIFIC AIMS. Asthma is the number one cause of pediatric emergency department (ED) visits in young children⁽¹⁻⁴⁾ and has a substantial impact on healthcare costs.⁽⁵⁻⁷⁾ Repeated ED visits for asthma care are not only costly but are an index of poorly controlled asthma.⁽⁸⁾ The ED is often the point of contact for low-income children^(8,9) with many families viewing the ED as their *primary* source of asthma care.⁽¹⁰⁾ In fact, there has been a recent decline in primary care outpatient visits for asthma.⁽²⁾ Unfortunately, low-income and minority children suffer the greatest morbidity from asthma and have the highest ED utilization,⁽¹¹⁾ yet are less likely to receive adequate preventive therapy and are more frequently exposed to environmental triggers compared to non-poor children.^(3,12-20) Low-income minority children with asthma receive suboptimal guideline based care partly due to lack of access to specialty care,^(14,15,22) lack of follow-up with their primary care provider (PCP) after ED visits,^(10, 24, 25-29) and/or insufficient delivery of guideline based care in the primary care office (i.e. no spirometry or allergy testing).⁽³⁰⁻³²⁾ Essential guideline recommendations for preventive asthma care include: assessment of asthma severity and ongoing control, appropriate prescription of inhaled corticosteroids (ICS), counseling regarding avoidance of allergen and irritant exposures, delivery of asthma action plans, scheduling follow-up asthma visits, and provision of self-management education.⁽²¹⁾ However, these recommendations are unlikely to be delivered in the context of an acute ED asthma visit.⁽²²⁾ New models of care are needed to transition care for young minority children from the ED to primary care who are unlikely to follow-up in primary or specialty care clinics so that they may receive guideline-based care.

Our prior asthma communication intervention included a PCP and caregiver feedback intervention targeting children with frequent asthma ED visits and demonstrated increased preventive medication adherence,^(25, 33-34) but no change in PCP follow-up rates. We also detected exposure to high levels of second hand smoke (SHS) and other environmental triggers, yet these children had low rates of specialty care.^(23,25, 33-36) To address these challenges, we adapted and piloted a program to provide optimal follow-up for these high-risk children *in the ED setting and 3-5 days after index ED visit*,⁽³⁷⁾ that it is accessible for families to attend and added collection of biomarkers of SHS and allergy, a home environmental control component and use of feedback communication with PCPs and caregivers. Our pilot data confirm high attendance at a single ED follow-up visit, participation in the home environmental component and use of feedback communication.

The over-riding goal of the **Asthma Express (AEx)** study is to build upon our prior work by testing the efficacy of a behavioral intervention that links **emergency, primary and home based care to provide coordinated preventive care for children with frequent asthma ED visits** in order to reduce asthma morbidity, subsequent ED visits and hospitalizations. The **AEx** intervention includes (1) collection of biomarkers of SHS exposure and allergen sensitivity during the index asthma ED visit,(2) a follow-up visit *in the ED setting* for a “mini-specialist” evaluation within 5 days of the index ED visit to include a) asthma evaluation and education, b) prescription and/or adjustment of ICS medication, c) review of allergy and cotinine results, d) provision of an asthma action plan, (3) delivery of a home visit within 2 weeks of index ED visit to deliver environmental control program tailored to the child’s allergy and cotinine results, (4) communication with PCP and caregiver via “feedback letters” including allergy, cotinine, pharmacy refill results with guideline based recommendations and (5) scheduling a PCP appointment for asthma follow-up. The **AEx** intervention will be compared to an attention control (CON) group receiving only asthma education.

Specific Aims of the study are:

Aim 1. To reduce asthma morbidity defined as number of symptom days and nights (primary outcome), missed school days and caregiver work absences due to asthma, ED visits and hospital days and **increase** caregiver quality of life (QOL) and improved child asthma control. **H 1.** Children in the AEx intervention group will experience significantly higher symptom free days/nights (primary outcome) and improved asthma control and decreased ED visits, hospital days, missed school days and **caregivers** will

have decreased work days missed and increased QOL compared to children/caregivers assigned to the CON group.

Aim 2. To improve the use of appropriate anti-inflammatory (controller) medication (receiving ≥ 6 controller medication refills/12 months or achieve a controller-to-total (C-T) medication ratio >0.5) based on national asthma guidelines.⁽⁸⁾ **H2:** Significantly more children receiving the AEx intervention will have ≥ 6 controller refills over 12 months or C-T ratios ≥ 0.5 compared to children in the CON group.

Aim 3. To compare the economic cost and effects of this intervention. We will compare costs and monetized health benefits of the AEx intervention with the CON intervention using a societal perspective.

H 3. Per child costs of the AEx intervention, asthma-related medical and lost productivity, will be less than the asthma-related medical care costs and lost productivity for children receiving the CON intervention.

Impact: This novel, cost-effective and reproducible intervention promotes the delivery of guideline based asthma care by linking the ED, primary care and home setting to reduce morbidity among high-risk urban children with asthma and uses allergy and cotinine biomarkers to target home environmental control.

2. RESEARCH STRATEGY

2.A. SIGNIFICANCE

Rationale for targeting young minority children with frequent ED visits. Asthma affects 7.1 million US children and is the number one cause of pediatric emergency department (ED) visits.^(1-4, 38) Children with frequent ED visits are at the greatest risk for life-threatening asthma, decreased quality of life and increased school absences.⁽³⁹⁻⁴²⁾ Most cases of chronic asthma begin in preschool years.⁽⁴³⁾ Low-income, African American children have 4.1 times higher ED visits and a death rate 7.6 times higher than rates of non-Hispanic white children.⁽³⁾ Despite the disproportionately high morbidity and mortality from asthma,^(11,44) minority low-income children are the least likely to receive adequate guideline based therapy,^(12,13,45) and specialty care for asthma.^(14,15,23,34)

Preventive Asthma Management: Expert Panel Report (EPR- 3) Guidelines Implementation^(8,21)

Airway inflammation is a key component of asthma.^(8,21) Inflammation and airway remodeling can occur early in asthma and may lead to long-term loss of lung function and impairment.⁽⁴⁶⁾ The cornerstone of preventive care is regular use of anti-inflammatory medications, including inhaled corticosteroids(ICS) that modify several components of the inflammatory process including the generation of cytokines, recruitment of airway eosinophils and release of inflammatory mediators.⁽⁴⁶⁻⁴⁹⁾ Anti-inflammatory medications, including inhaled corticosteroids (ICS), are the most effective medications to help establish long-term control of asthma^(8, 49-50) and reduce ED visits and exacerbations.⁽⁵¹⁾ Despite these positive effects of ICS, under-utilization of ICS remains high in underserved children with asthma^(12, 52-54) with < 50% of children presenting to an ED for asthma taking an ICS.^(51,55) Additional critical guideline-based preventive measures for asthma control include initial assessment of asthma severity, ongoing assessment of asthma control, environmental control education, home remediation for allergen and irritant exposures, use of asthma action plans and planned follow-up asthma visits.⁽²¹⁾ However, provision of preventive asthma care is striking low in minority children. Only 31% receive preventive medication, 23% are seen by a specialist, 44% receive a written asthma action plan and only half (50.6%) receive advice regarding environmental control.⁽⁵⁶⁾ Access to specialty care has been associated with long-term control of asthma resulting in decreased asthma morbidity and ED visits⁽⁵⁷⁾ and increased quality of life,^(5,8,22, 56,58-59) yet access for poor children is low.⁽⁵⁶⁾

Gap in linking ED to Primary Care for Children with Asthma The ED is often the point of contact for urban children with asthma⁽²⁶⁻²⁷⁾ for both acute and chronic asthma management.⁽⁶⁰⁾ Although national asthma guidelines recommend follow-up after an ED asthma visit within 1 to 4 weeks with a primary care provider,⁽⁸⁾ adherence to follow-up care after an ED visit is striking low particularly among high risk inner city populations.^(10, 23, 27) This results in a “missed opportunity” for children to receive preventive medications.^(28,49,61) Only 60% of inner city children with persistent

Legend

AEx: Asthma Express Intervention
ACE: Asthma Communication Education study (NR008544)
CON: Control group
ED: Emergency Department
ICS: Inhaled corticosteroid med
PAAL: Pediatric Asthma Alert Intervention Study (NR010546)
PCP: Primary Care Provider
PNP: Pediatric Nurse Practitioner
SABA: Short acting beta agonist
SHS: Second Hand Smoke

asthma received adequate ICS pharmacy fills, yet had a mean of 1.8 ED visits over a 12 month period in our prior data. ^(25, 52) ED physicians/health care providers commonly do not prescribe ICS medications ⁽⁶²⁾ nor evaluate environmental exposures during the ED visit due to belief that this is the role of the PCP or asthma specialist. ⁽²²⁾ Yet prior studies indicate that only 52-56% of young inner-city children were evaluated by their PCP within 1 month following an ED asthma visit or used preventive asthma medication. ⁽⁶³⁻⁶⁴⁾ Several ED-based interventions to improve primary care follow-up have been tested. Children who received allergy skin testing with results during an asthma ED visit were 2.6 times more likely to keep an asthma clinic appointment than non-tested children (95% CI 1.02-6.65). ⁽⁶⁵⁾ In a randomized controlled trial of 433 children attending an ED asthma visit, intervention parents viewed a video during the ED visit that addressed beliefs and barriers to follow-up primary asthma care plus received a letter about the ED visit care of the child to be delivered to the child's PCP and a reminder call about the PCP visit as compared to controls who were reminded to follow-up with their child's PCP. ⁽⁶⁶⁾ Notably, median time to PCP follow-up was 38 days in both groups and rate of PCP follow-up at 4 weeks did not differ between groups (INT: 44.5%; CON: 43.8%). ⁽⁶⁶⁾ Initiation of ICS medication during an asthma ED visit plus a call to the child's PCP to obtain approval of the medication and faxing a letter with the proposed treatment plan, resulted in a 70% PCP follow-up rate in a convenience sample of children with persistent asthma who were not previously prescribed ICS medications. ⁽⁶⁷⁾ An ED-based educational computer intervention with a tailored component based on family/child needs plus receipt of an asthma action plan and a PCP appointment reminder call as compared to usual care resulted in intervention children more likely to attend a primary care asthma visit at 9 months (OR 1.85; 95%CI:1.05-3.39) than control children, yet the follow-up rate remained low (40-52%). ⁽⁶⁸⁾ Additional strategies to link ED to primary care for children with asthma have demonstrated limited success such as scheduling a PCP follow-up during the ED visit, ⁽⁶⁴⁾ reminder phone calls for PCP appointments, identifying a new PCP if the child is not linked to a PCP, and facilitating child care and transportation to the PCP. ⁽⁶⁹⁻⁷¹⁾ Even using an asthma coach during an ED visit combined with a \$15.00 incentive to adhere with a PCP appointment failed to increase PCP follow-up rates after the index ED visit. ⁽⁷²⁾ These studies suggest that a more intensive ED-based intervention, i.e. providing a mini "specialty care" follow-up visit may result in a larger impact on linking ED to preventive asthma care for children with frequent ED visits.

Why Link Home-based Environmental Control into ED-based interventions? Asthma morbidity is often a result of interactions between genes and environments. ^(73, 74) Low-income children are more frequently exposed to environmental triggers than non-poor children ⁽¹⁶⁻²⁰⁾ including high levels of indoor allergens ⁽⁷⁵⁾ and SHS. ^(23,35) Allergen sensitivity and exposure are associated with increased asthma morbidity, particularly in sensitized individuals with asthma. ⁽⁷⁶⁾ In general, 60-79% of children and young adults with asthma test positive for at least one airborne allergen ⁽⁷⁷⁾ yet in a recent study conducting skin testing during asthma ED visits, 100% of children reacted to at least 1 allergen. ⁽⁶⁵⁾ Modifying the indoor environment to reduce particulate matter, allergen exposures and nitrogen dioxide is suggested to reduce asthma morbidity ^(78,79) however many studies are inconclusive. Exposure to allergens and irritants is high in inner city children due to substandard housing conditions that results in exposure to high cockroach and mouse allergen levels ^(16,80,81) and increased time spent indoors due to neighborhood violence. Moreover, 40-67% of inner-city children with asthma reside with at least one smoker. ^(16,23,82,83) These exposures are associated with asthma exacerbations and ED use. ⁽⁷⁵⁾ Almost half (45%) of families in our current study (NR010546) reported mice and 28% cockroach infestation in their homes, yet only 33% reported knowing if their children had received allergy testing. Receipt of specialty care by children with asthma is associated with significant reduction in asthma ED visits, hospitalizations and school days missed ⁽⁵³⁾ however, poor and minority children with persistent asthma are less likely to receive specialty care than non-poor white children ^(14,15) and is strikingly low for Baltimore children at 19-24%. ^(31,33-34) Intensive environmental control education and home remediation is one major component of asthma specialty care for children. ⁽⁸⁴⁾ Few inner-city children receive the benefit of environmental interventions based on their sensitization and exposure profiles. ⁽⁶⁵⁾ **Thus, multifaceted, individualized interventions that link the emergency, primary care and the home environment are needed to reduce asthma morbidity and high health care cost in children with frequent ED visits for asthma.**

Impact. Asthma is the number one cause of pediatric ED visits, yet adherence to preventive care is low at 22-56% posing a serious public health problem. Because the ED often is the primary point of contact for

urban children with asthma⁽²⁶⁾ for both acute and chronic asthma management,⁽⁶⁰⁾ bridging the gap between the ED, primary care and the home environment is paramount to reducing asthma morbidity. Prior childhood asthma ED-based interventions have reduced unscheduled visits⁽³⁷⁾ yet few have improved adherence to scheduled PCP visits for preventive care or addressed environmental control. **Linking emergency, primary and home-based care to provide early preventive care in children with frequent ED visits for asthma to reduce asthma morbidity and healthcare costs is significant, innovative and is consistent with current guideline recommendations for asthma care.**

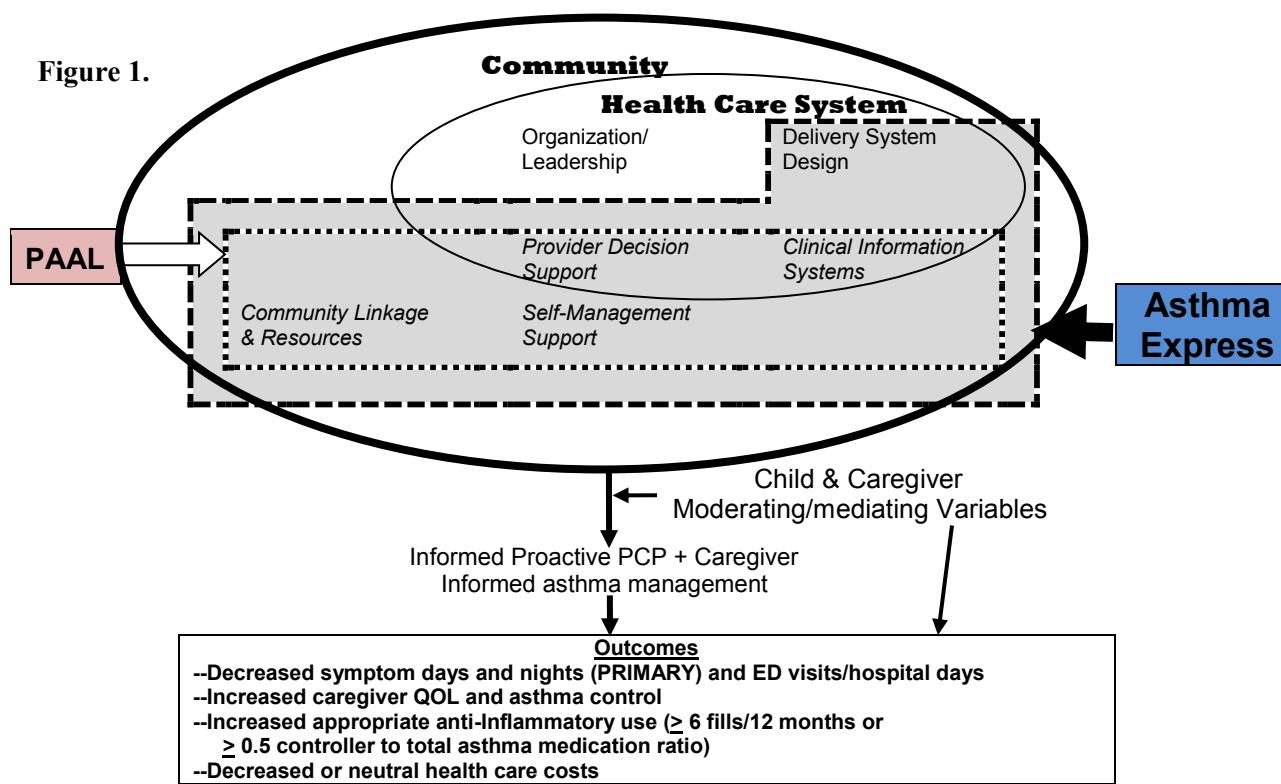
2.B INNOVATION: The project's innovative strategies include: (1) initiating preventive asthma care immediately following an asthma ED visit in an accessible location (ED), (2) use of biomarkers collected during ED visit to identify the child's allergen and SHS exposure profile, (3) providing a "mini-specialist" clinic visit at ED follow-up (allergy, cotinine and spirometry testing with specialist consultation) conducted by nurse practitioners with real-time allergy and pulmonology consultation and (4) providing a home visit component for individualized environmental control education and remediation based on allergen and SHS biomarker results collected during ED visit. The **AEx** model is designed to be accessible, guideline-based, easily replicated and incorporated into ED care. The *AEx intervention is translatable across settings, i.e. rural, community-based, non-academic health centers since the intervention is staffed by nurses and nurse practitioners with access to specialty consultation, use standardized forms (national guidelines, asthma action plans, asthma control tests) and use tests (Spirometry, RAST) and environmental control products (mouse traps, mattress encasings) that are widely available and used outside major health centers.*

2.C. Public Health Impact: Recent studies of inner-city children with asthma indicate that only 22-56% of children attending an ED for acute asthma exacerbations receive follow-up care for asthma.^(66,85) The results of this study are likely to result in offering patients and insurers a bridge between ED acute care, primary preventive care and home environmental control. This bridge will provide several components of intensive asthma care to inform ongoing preventive care by providing the PCP with health data including allergy sensitization and cotinine test results, recommendations whether to modify ICS medications when appropriate and implementing targeted environmental control remediation in the home. This proposal will provide rigorous data on the efficacy of the AEx intervention worthy of insurers review for use in EDs for children with asthma.

2.D. Conceptual Framework based on Wagner Chronic Care Model and Patient Centered Care

The framework for this study was adapted from Chronic Care Model (CCM)⁽⁸⁶⁻⁸⁹⁾ and patient centered care.⁽⁸⁷⁾ The CCM is a primary care based framework aimed at improving care of patients with chronic disease⁽⁸⁶⁻⁸⁹⁾ and promotes productive interactions between providers and patients.⁽⁹⁰⁾ Because the Asthma Express intervention involves a delivery system change, i.e. ED-based asthma follow-up and community linkage and resources we chose the Chronic Care Model. Core elements of the CCM include the health care system (organization/leadership, delivery system design, clinical information systems, provider decision support) and the community elements of self-management support, and community linkage & resources. The CCM model (Figure 1) demonstrates that the health care system exists within the larger community (dark circle) that includes community resources and self-management support.

Figure 1.



Our current Pediatric Asthma Alert (PAAL) intervention targets Provider Decision Support, Clinical Information Systems, Community Linkage and Resources and Caregiver & Patient Self-Management Support in the model (small dotted line). **The AEx (dashed lines) adds the Delivery System Design and strengthens the Community Linkage and Resources.** Under the Delivery system design, the ED-based follow-up visit, includes a “mini-specialist” visit and links the child’s ED care to the child’s PCP and the home. We will electronically relay the child’s medical asthma information to the child’s PCP (clinical information system) to enhance provider decision support to implement guideline based care. The home-based environmental control component, targeting the child’s allergy and cotinine results, provides linkage to community resources; the Baltimore City Health Department for free smoking cessation programs, rat control and housing services. Both the self-management and provider decision support activities are strong determinants of health outcomes ⁽⁸⁷⁾ and remain strong components of the **AEx**. The CCM is fundamentally concordant with **patient centered care** and is tailored to patient preferences, values, readiness and incorporates prevention in asthma care. ^(87, 91) The outcomes may be moderated or mediated by **caregiver and child variables** including caregiver age, depressive symptomatology and stress, and child age, asthma severity and control, SHS exposure and allergy status.

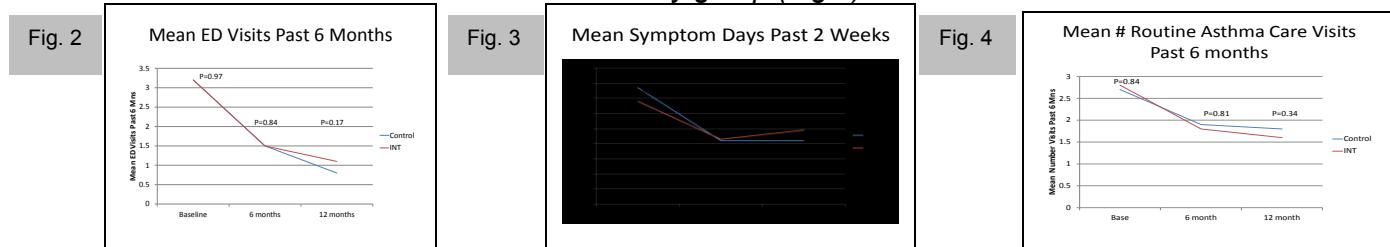
2.E. Preliminary Studies. This proposal describes an ambitious project led by a highly experienced, multidisciplinary team (Butz, Bollinger, Frick, Kub, Ogborn and Tsoukleris) who have worked together on multiple projects addressing high risk children with asthma during the past 12 years. Drs. Mudd, Oeklo and Teach complement the team with expertise in ED-nursing, pulmonology and ED-based interventions.

2.E.1. Predictors of frequent ED use and underuse of Inhaled corticosteroid (ICS) medication. (Butz-P.I.) Our prior studies had demonstrated that high rescue medication use and high caregiver depressive symptoms are associated with frequent ED utilization. In our study of 221 young minority children with asthma using a nebulizer (Nebulizer Education study, NR05060), high rescue medication use (poor asthma control) was associated with increased ED use ($p=0.04$) ⁽⁵²⁾ Further, children enrolled in an asthma communication study (ACE NR008544) with high rescue medication use were 2.7 times more likely to have a caregiver reporting high depressive symptoms ⁽⁹²⁾ that may impair the caregiver’s home management of their child’s asthma resulting in ED utilization. Underuse of anti-inflammatory medications has been a consistent finding in our studies. Only 20% of children with persistent asthma received appropriate controller

medication refills (≥ 6 ICS refills/12 months) at baseline, yet most children had ≥ 2 PCP visits/opportunities to receive anti-inflammatory medication.^(25,52) In our PCP and caregiver feedback intervention study of 300 minority children with persistent asthma, mean ICS fills/12 months for all participants were low at baseline: 4.3 (SD 4.0) despite high mean short acting beta agonist (SABA) use of 3.8 fills/12 months (PAAL NR010546). This suggests ICS underuse and poorly controlled asthma based on SABA use. At 12 months follow-up, mean ICS fills did not differ by group (INT: 4.1 fills (SD4.): CON: 4.0 fills SD4.4, $p=0.90$). In the same study, mean ICS fills were not associated with distance to pharmacy although families using one pharmacy had the highest mean ICS fills (3.0, SD2.7).⁽⁹³⁾ Caregiver stress and depressive symptoms may be other predictors of frequent ED use. In the PAAL study, caregivers encountered multiple life stressors that may decrease their capacity to appropriately manage their child's asthma resulting in ED use.⁽⁹⁴⁾ (APPENDIX B-Bellin) Common caregiver stresses were threat of utilities/phone cut off (51%), rats, mice, or insects in the home (49%) and neighborhood violence (38%).⁽⁹⁴⁾

2.E.2. Emergency Department-Based Randomized Trial to Improve Asthma Outcomes in High Morbidity Pediatric Population. IMPACT-DC (Teach-P.I.) To test the effectiveness of a single follow-up visit in the ED following an acute asthma exacerbation treated in the ED, 490 children were randomized into 2 groups: Control (CON) or standard care ($n=244$) versus Intervention (INT) of a single follow-up visits in the ED ($n=244$).⁽³⁷⁾ This ED based intervention focused on asthma self-monitoring and education regarding management, environmental modification and trigger control with linkages and referrals to preventive care. Within the INT group 172/244 (70.5%) attended the follow-up ED visit. At 6 months, the INT group had a significantly higher percent of ICS use in the prior 2 days (INT: 49.3% vs. CON: 26.5%, $RR=2.03$) and significantly fewer mean unscheduled visits for asthma (INT: 1.39, CON: 2.34, $RR=0.60$).⁽³⁷⁾ The AEx intervention builds on the IMPACT-DC model with the addition of (1) collection of allergen (RAST) and cotinine biomarkers at index ED visit, (2) PCP and caregiver feedback including RAST and cotinine results and (3) a home environmental control component individualized for the child's allergen and cotinine results.

2.E.3. Feedback/Prompting of child health information to PCPs and parents. (PAAL, NR010546), (Butz-P.I.). In our recently completed PCP and caregiver feedback study of 300 young children with frequent asthma ED visits, intervention children (INT) had a nurse prompt their PCP to prescribe an ICS medication when indicated and communicate cotinine levels and pharmacy fill data to the PCP via feedback letter. Outcomes were compared with an attention control group (CON). At 6 months, medication adherence was significantly higher in the INT group (High adherence: INT: 89.6%, CON: 81.4%; $X^2 = 3.82$, $p=0.05$) and INT children reported significantly higher asthma control based on days of wheezing over past 4 weeks (≤ 3 days wheezing for asthma control: INT: 64%, CON: 57% ($p=0.04$). However, mean ED visits, symptom days or ,number of routine PCP asthma visits did not differ by group at 6 or 12 months (Fig 2-3) At baseline, the overall mean number of symptoms days/past two weeks was 7.24 (SD 5.31) and decreased to 4.34 (SD 4.69) at 6 months and 4.53 (SD 5.0) at 12 months. Mean number of PCP asthma visits decreased from 2.7 at baseline to 1.7 at 12 months with no difference by group (Fig 4).



Follow-up was high at 6 months (95%) and 12 months (91%). Successful delivery of the PAAL intervention (PCP and home visit) occurred in 71% of children (Appendix B-Butz) and exceeds PCP follow-up rates of most ED-asthma intervention studies. Younger child age (OR: 4.7, CI2.1,10.7), having an asthma action plan (OR: 3.0, CI 1.2,7.5) and lower caregiver daily asthma stress(OR: 0.89, CI 0.79,1.0) were significantly associated with completion of a PCP visit in regression analysis, while adjusting for medication adherence, caregiver depression and controller medication use. Lessons learned from PAAL: 1) caregivers of older children need accessible hours for follow-up, i.e., after school and weekends, 2) high caregiver stress is a marker of poor follow-up; and 3) lack of asthma action plan may be marker of poor preventive care. Asthma

Express builds on the IMPACT-DC and PAAL studies by combining an ED based intervention and PCP communication to have a greater impact on asthma control in high risk inner city children with asthma.

2.E.4. Identifying the burden of SHS and measuring SHS exposure in urban children with asthma. (Particulate Reduction Education in Childhood Asthma study EPA: P01 R-826724/NIEHS:E09606) and PAAL feedback study (NR010546) (Butz-P.I.) In a randomized 3-arm controlled trial we examined the efficacy of an air cleaner and health coach intervention in reducing particulate matter in homes of children with persistent asthma and who resided with a smoker.⁽³⁶⁾ Results showed that particulate matter (PM) _{2.5} levels were high (Mean PM _{2.5}: 30.7 $\mu\text{g}/\text{m}^3$ (standard: $\leq 15 \mu\text{g}/\text{m}^3$) in homes of study children living with a smoker. Caregivers were the primary smoker (68%); smoking occurred primarily in family room (50%) and caregiver bedroom (46%).^(35,36) High SHS exposure was also noted in the PAAL study with positive salivary cotinine level ($\geq 1.0 \text{ ng}/\text{ml}$) detected in 60% children at baseline⁽²³⁾ and 56% at 12 months. No difference in mean cotinine level by INT vs. CON group were detected at 6 or 12 months. The child's caregiver and spouse were the predominant smokers in the home (70%) and younger children (3-5 years) had significantly higher cotinine levels than older children even with a total home smoking ban.⁽²³⁾ These findings support the home environmental control component of the AEx intervention to coach caregivers how to institute a total home smoking ban.⁽³⁶⁾

2.E.5. Cost Effectiveness Analysis. (Butz-P.I.) Prior cost effectiveness analysis conducted in the Asthma Communication Education study (ACE, NR008544) demonstrated no cost-saving of the intervention. (Table 1). Costs were measured from the perspective of the health care payer and the patient. The increased pharmacy cost in the intervention group is most likely related to increase controller medication fills. Although the intervention group had higher expenses in pharmacy, ED and inpatient costs, all differences were not significant by group ($p > 0.05$ for all comparisons). High SDs reflect high utilization in subgroup of children.

Table 1. Asthma Related Cost	ACE Intervention Group N=99 Mean (SD) \$	Control Group N=91 Mean (SD) \$
Inpatient cost	1,690 (5,797)	1,282(10,634)
ED cost	384 (1,215)	193 (262)
Outpatient cost	413 (581)	316 (354)
Pharmacy cost	1,040 (1,293)	748 (1,110)

2.E.6. Asthma Express (AEx) Pilot Study. (Butz-P.I.) A total of 32 out of 58 eligible children were recruited and enrolled in the Asthma Express pilot intervention (INT) study during their asthma ED visit. The original pilot had 15 children and we recruited 17 additional children to test the full intervention. A separate group of 25 historical control children (CON) were matched for child age, race and date of ED visit. Data for CON children were abstracted from medical records using a HIPAA waiver approved by the JHMIRB and included number of ED visits, hospitalizations and PCP visits over the 2 month follow-up period. Children were primarily male (67%), African American (97%), Medicaid insured (97%) and young (mean age 5.7 years). Morbidity was high in INT group; mean symptom days and nights/past 30 days were days: 8.63(SD9.2) and nights: 9.78(SD 10.6). Many (38%) reported daily use of albuterol over the last 4 weeks indicating poor asthma control. At baseline, INT children had a mean of 2.2 (SD 3.6) ED visits during the last 12 months, yet 38% reported no PCP visits over past 6 months. Attendance at the pilot Asthma Express clinic was high at 72% (23/32) and most attended the AEx clinic within 6 days of the index ED visit. Overall 81% of children received an AEx visit or one home visit indicating high delivery of the AEx intervention.

During the AEx visit 25% children had diffuse expiratory wheeze but none required acute ED treatment. Mean baseline cotinine levels were high at 2.02 $\mu\text{g}/\text{ml}$, (SD1.9) and (58%) had cotinine levels $\geq 1.0 \mu\text{g}/\text{ml}$ indicative of SHS exposure. 80% of children who had at least one positive RAST test, consistent with the 78% previously reported in other inner-city populations.^(77, 95) Common positive RAST tests were dog (72%), cat (64%), oak tree (56%), house dust mite (52%), cockroach (50%), and mouse (45%). Spirometry was performed with 42% of children; young age precluded collection of spirometry data on the other 58%. Problem indoor exposures noted on home visits were person smoking during nurse visit (35%), dustmite problem (43%), mouse droppings + cockroaches (42%), and any evidence of mouse in home (50%). One-third of homes had a cat to control a mouse problem. At the 2 month follow-up 50% of INT children reduced their positive cotinine level (≥ 1.0) to negative level (<1.0) although this was not significant ($\chi^2=1.53$, $p=0.2$). INT children were more likely to have a PCP visit than CON children (INT: 54%; CON: 40%, $p=0.32$) and less likely to have an ED visit over the 2 month follow-up (INT: 16%; CON: 32%, $p=0.16$) yet both were not statistically significant. A trend was noted with more INT children reporting asthma is controlled over the follow-up (Asthma Controlled: INT: 68%, CON: 48%, $p=0.1$). These studies demonstrate our ability to

conduct the proposed AEx intervention, indicate high to moderate success in piloting the intervention and highlight our extensive multidisciplinary long-term experience in conducting randomized controlled trials of behavioral interventions for minority children with asthma.

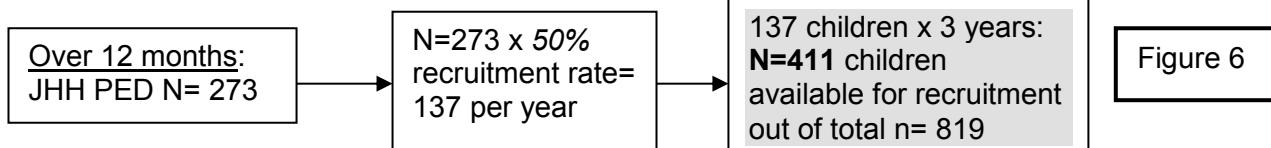
3.0 APPROACH: DESIGN and METHODS

Overall Design: The proposed study is a two-group randomized controlled trial designed to evaluate the efficacy of a multifaceted ED-based asthma intervention to reduce asthma morbidity and subsequent asthma ED visits, increase appropriate anti-inflammatory medication use and reduce cost care or be cost neutral. We will consent and enroll 264 children aged 3-12 years with persistent asthma and who have ≥ 2 asthma ED visits or 1 hospitalization over the past 12 months. Caregivers are consented in the Johns Hopkins Hospital Pediatric ED (JHH PED) during the child's asthma ED visit. Once consented, all children receive allergy testing (RAST test-5 ml blood) and cotinine concentration measurement (1 ml saliva) and then randomized to either the AEx or attention control (CON) group using a block design and stratified by age group of 3-6 and 7-12 years. Children and their caregiver are followed for 12 months. Surveys will be administered at baseline, 3, 6, 9, and 12 months to collect demographic, asthma health, medication use, maternal caregiver depression, QOL and stress, smoking characteristics of the household data. (APPENDIX C) Subjects will be remunerated at \$30.00 for baseline, 6 and 12 months and \$10.00 for each 3 and 9 month survey. A home inspection of indoor environmental exposures for data purposes only, will be collected at baseline and 12 months by RA or interviewers. (APPENDIX D). *The AEx intervention consists of one ED follow-up visit and two home visits by AEx home visiting nurse over 8 weeks.* For families who relocate over the 8 week intervention, an additional home visit will be conducted in the new location. The CON group receives 3 home visits for basic asthma education over 8 weeks as an attention control and the caregiver and PCP receive the child's RAST and cotinine results after completion of CON visits. (Figure 5)

Figure 5. Intervention and Data Collection Timelines

(HV= Home visit, ED=ED follow-up Home=home or tele=telephone interview)								
Baseline ED Visit	3-5 days	4 wks	6wks	8wks	3mn	6mn	9 mn	12 mn
Interventions								
AEx	ED follow-up	1 st HV	2 nd HV		(AEx: Asthma Express Targeted Home Visits)			
CON	1 st HV	2 nd HV	3 rd HV		(CON: Community Health Nurse Visits)			
Data Collection								
Questionnaire					Tele	Home	Tele	Home
RAST test								
Cotinine					Cotinine		Cotinine	
Pharm Data							Pharm Data	
Home Inspection							Home Inspection	

Sampling Design: The sample population will include 264 children with persistent asthma and ≥ 2 ED visits or 1 hospitalization for asthma during the past 12 months and their caregiver. In 2011, the pediatric population served by the JHH PED was 89% African American and Medicaid insured (87%). We anticipate few Hispanic families to be eligible for this study in that persons of Hispanic origin accounted for only 4.2% of Baltimore residents in 2010. ⁽⁹⁶⁾ If a Hispanic child has an asthma ED visit they will be recruited. The JHH PED, a new 34 bed ED unit, has over 26,600 visits per year. In 2011, there were 11,069 visits for children aged 3-12 years and 1545 patients aged 3-12 years were treated for asthma and wheezing (code 493.9, 493.91, 493.92, 786.07) at the JHH PED. Of the 1545 patients, 263 had ≥ 2 ED visits or were hospitalized over past 12 months (n=10) for total n=273. We anticipate a *50% recruitment rate based on our pilot study* at 137 children age 3-12 years per year or 411 children over the 3 year recruitment period. This is more than sufficient to meet our sample size of 264 children (n=132 per group). Figure 6.



Inclusion criteria are (a) physician diagnosed asthma, (b) ≥ 2 ED visits or ≥ 1 hospitalization for asthma within past 12 months, (c) mild to severe persistent asthma based on NHLBI guidelines criteria ⁽⁸⁾ (d) age

≥ 3 and ≤ 12 years, (e) reside in Baltimore metropolitan area, (f) caregiver ability to read at basic or 4th grade level, (g) not currently participating in an asthma study or sibling enrolled in AEx study. Reading level tested during consent process. **Exclusion Criteria:** (a) Inability to speak and understand English, (b) no access to a working phone for follow-up surveys, (c) co-morbid respiratory condition including cystic fibrosis, and other chronic lung disease and (d) children residing in foster care or where consent cannot be obtained from a legal guardian. We anticipate < 10% subjects will be excluded based on exclusion criteria.

Recruitment Procedures. We will recruit interested families of children with acute asthma using our prior HIPAA approved protocol for daily review of the JHH PEDS-ED census board for children with asthma. Dr. Ogborn, JHH PEDS ED attending physician or her alternate will seek permission from the child's caregiver to allow the master's prepared research assistant (RA) to discuss the study with the caregiver during the PEDS ED visit. We have budgeted for recruitment at 16/24 hours in the PED ED including weekends. Due to the extended ED time required for most children to resolve an acute asthma exacerbation, we will be able to recruit children arriving to the ED after 12:00AM during the following morning. If the parent agrees, the RA will explain the study, obtain informed consent, collect blood (RAST for allergy testing) and saliva (cotinine testing) from the child, administer the baseline interview, randomize each child to the AEx or CON group. For parents who refuse blood drawing in the PEDS ED, they will be provided an option to return the next day to the JHH pathology lab for drawing of the child's blood. In the PEDS ED, the RA will open a sealed randomization envelope. Caregivers and children randomized to the AEx group will receive an appointment to the AEx visit (within 3-5 days) (APPENDIX E). Children randomized to CON will receive an appointment for the community home asthma nurse to conduct the CON home visits. We achieved a 55% enrollment rate and a 79% rate of blood draw during the AEx pilot study.

Randomization: We will stratify the randomization for ages 3-6 (preschool) and 7-12 years (school age) to ensure comparable groups by age. Age stratification has been included in the sample size calculation. Since enrollment and randomization will occur over an extended time period, a permuted block design will be used to assure an equal balance of children in each age group for each seasonal time period. Using computer generated list of random digits, Dr. Thompson will develop the randomization scheme and prepare randomization cards in sealed opaque envelopes and sequentially numbered for use by the recruiter RA. Following completion of the baseline survey, each child will be randomly assigned to the AEx or CON group using the randomization cards in the numbered envelopes. Dr. Butz, co-investigators and interviewers will be blinded to group assignment.

Interventions. All children (AEx and CON) receive allergy and cotinine testing during their index ED visit. **(AEx) Intervention:** consists of five components addressing the six asthma guideline based priorities:⁽²¹⁾
(1) A "mini-specialist" follow-up visit within 3-5 days after index ED asthma visit delivered at the JHH PEDS ED by a pediatric nurse practitioner (PNP) with asthma expertise. This short clinic visit, scheduled in late afternoon or weekends to accommodate family schedules, will provide symptom monitoring, spirometry for children ≥ 6 years of age, specialized asthma education and an asthma action plan. (APPENDIX F) A prescription will be written for children without an ICS prescription and the medication delivered to the home by the Baltimore Northern Parkway Pharmacy to reduce one barrier to adherence. In children with asthma enrolled in school based asthma intervention, 70% had asthma medications delivered to both home and school⁽⁹⁷⁾ to reduce barriers to medication adherence. Medication vouchers will be provided to children with no health insurance. Specialized Asthma Education (device training, peak flow meter use, appropriate medication use and adherence) will be conducted with the parent and the child when developmentally appropriate. Asthma action plans will be reviewed and provided to the parent. Referrals for asthma specialty care will be made based on guideline criteria, i.e. severe asthma episode and after seeking PCP approval. Child's digital photo will be taken for inclusion on feedback letters. (Guideline Priority: Inhaled corticosteroids, Asthma Action Plan, Assessment of asthma severity, Assessment of asthma control).

(2) Delivery of a home environmental control program individualized to child's allergy and cotinine results delivered during 2 home visits over 8 weeks. *We believe that demonstrating environmental control techniques in the home will be more effective than environmental control education delivered at a PCP visit. A specially trained community health nurse, Mr. Lukk, BSN will conduct all INT home visits and served as our pilot home visit nurse. Mr. Lukk was trained in integrated pest management (IPM) and will conduct specific integrative pest management (IPM) practices in homes with identified rodent and cockroach*

infestations. He will refer families to appropriate community resources, i.e. alternative housing, rat control. During the home visit, families will receive green cleaning supplies, kitchen trash can + trash bags, mattress covers, and IPM supplies (roach baits, mouse traps) based on the child's RAST results and home assessment. For children with cotinine levels ≥ 1.0 , indicating SHS exposure, the AEx home nurse will provide counseling using a "health coach" protocol to institute a total home smoking ban. (36,96-98) A motivational ladder and contingency contract will be used (APPENDIX G, Home visit protocol forms). Additionally, a "Safe Zone" will be identified and taped off for smoking outside of the home. Health coach interventions are effective in reducing SHS exposure in homes of children (36, 98-102) and enhance medication adherence in adolescents with asthma. (103) Children with negative RAST and cotinine results (expected < 10%) will still receive home visits for preventive environmental control education. (Guideline Priority: Avoidance of allergen and irritant exposure)

(3) PCP "Feedback letter" (APPENDIX H) electronically sent and faxed to child's PCP that includes child's allergy and cotinine results, number of ED visits past 6 months, medication and peak flow meter device technique, pharmacy data for number of ICS and SABA fills, asthma control level, spirometry results for children ≥ 6 years, and environmental control procedures implemented in the home. The letter provides the PCP with guideline based recommendations for management including initiation or modification (step-up, step down) of ICS medication dose if indicated. Feedback letters will be reviewed/signed by Drs. Bollinger and Butz. (Guideline Priority: Assessment of asthma severity and asthma control, Inhaled corticosteroids)

(4) Parent "feedback letter" (APPENDIX H) with allergy and cotinine results and recommendations for each positive allergen and home remediation of SHS exposure delivered by AEx home nurse and caregiver understanding of the information included in the feedback letter will be verified during the 2 home visits. (Guideline Priority: avoidance of allergen and irritant exposure) and

(5) A Scheduled appointment with child's PCP made during the AEx visit linking the child to ongoing PCP care. If the AEx -PNP is unable to schedule an appointment during AEx visit, the PNP will schedule a PCP appointment the next day and call the parent with appointment date/ time. Text or phone reminders for PCP visit will be conducted by the AEx PNP and AEx home nurse. (Guideline Priority: planned follow-up visits).

Attention Control (CON) Intervention consists of 3 home visits over 8 weeks conducted by a different community health nurse to deliver basic asthma education comparable to standard asthma education received at a PCP visit and consistent with the NAEPP guidelines.⁽⁸⁾ (APPENDIX I) Specific content of CON visits: 1) pathophysiology of asthma , 2) use of rescue and controller medications, and 3) importance of preventive asthma follow-up with PCP, but no scheduling of PCP visits. At the end of the 8 week CON intervention, each CON family will receive a letter with their child's allergy and cotinine results and recommendations for avoidance of positive allergens. For children with baseline cotinine levels ≥ 1.0 ng/ml, the letter will include community resources for free smoking cessation programs. A copy of this letter will be sent to the child's PCP if family requests. Training and supervision of the CON nurse will be conducted by Drs. Butz and Kub.

Variables and Measures. Table 2.

Study AIM	Measurement/Instrumentation	Data Collection Schedule
Major Dependent Variables		
AIM 1. To reduce asthma morbidity defined as <u>increased</u> symptom free days and nights, <u>decreased</u> ED or urgent care visits for asthma, days of hospitalization, missed school days and caregiver work absences due to asthma and <u>increased</u> caregiver QOL and child asthma control.	<p>Symptom days and nights (continuous) (104-106) ED visits –medical record review* and self-report (107) Urgent care visits –medical record* and self-report (104-106) Hospital days-medical record* and self-report (104-106) Missed school days , Caregiver work absences due to asthma (104-106) Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ). (108) The intraclass correlation coefficient (ICC) was 0.85 for overall quality of life. ICC for the emotional function domain was 0.80 and 0.84 for the activity of limitation domain. (108) Asthma Control Test⁽¹⁰⁹⁾ (test-retest reliability $r=.77$; criterion validity demonstrated by significant associations with clinicians' ratings of asthma control ($r=.72$)⁽¹⁰⁹⁾</p>	Baseline, 3, 6, 9 and 12 months Medical record review at baseline,6 & 12 months (Electronic medical record)

Study AIM	Measurement/Instrumentation	Data Collection Schedule
AIM 2. To improve the use of appropriate anti-inflammatory (controller) medication (receiving ≥ 6 anti-inflammatory medication refills/12 months or controller to total medication ratio > 0.5) based on national asthma guidelines⁸	Number of anti-inflammatory refills (inhaled corticosteroid, leukotriene modifier, combination ICS +long acting β -agonist) Pharmacy refill data- collected from pharmacies ⁽¹¹⁰⁾ Controller to total medication ratio = #controller medication filled past 12 months/ controller + rescue medication fills last 12 months ^(110, 111) Electronic pharmacy data available for Priority Partner patients (85% JHH Peds)	Baseline, 6,12 mn Pharmacy data from individual and corporate pharmacies.
AIM 3. To compare the economic cost and effects of the intervention.	Health and economic benefits of the AEx intervention (symptom free day cost, medication costs ED visit and hospitalization cost) compare to cost of the AEx intervention (AEx follow-up visit costs (\$198) + cost of home environmental control component (\$311).	Baseline + 12 mn
Major Independent Variable		
Group status: AEx vs. CON	Randomization record file (categorical)	Baseline
Mediators and Moderating Variables		
Demographic factors: Caregiver: age, education, marital status, race/ethnicity Child: age, gender, race/ethnicity	Baseline Demographic Questionnaire	Baseline
Caregiver Depression	Center for Epidemiological Studies-Depression Scale (CES-D) ⁽¹¹²⁾ Cronbach's alpha = .86 in a community-based sample of mothers of youths with asthma; 4-week test-retest reliability $r = .67, p < .05$ ⁽¹¹²⁾	Baseline, 6,12 mn
Caregiver Stress	Perceived Stress Score (PSS4) ⁽¹¹³⁾ The reliability of the instrument is high (alpha coefficient = 0.85). ⁽¹¹³⁾	Baseline, 6, 12 mn
Allergy status	RAST test: 5 ml blood. Venipuncture by PEDS ED nurse or Pt care tech. OPTION: Child return to JHH lab/ Lab Corp at 1-3 days after ED visit.	Baseline: ED visit
Child exposure to second hand smoke (SHS)	1ml saliva, collected using sorbettes and swabs Salivary Cotinine Level ⁽¹¹⁴⁻¹¹⁷⁾ < 1.0 ng/ml =none to low exposure (>1.0 ng/ml = positive cotinine) 1.0-2.0 ng/ml=moderate exposure 2.0-4.5 ng/ml high exposure	Baseline: ED visit; 6 + 12mns collected in the home
Child Asthma Severity	Baseline questionnaire using NAEPP Guidelines ⁽⁸⁾	Baseline

Data Collection. Administration of questionnaires by interviewers blinded to group assignment, occurs at baseline, 3, 6, 9, and 12 months. We are using Research electronic data capture (REDCap) data collection and entry system using iPads for all questionnaire data to reduce data entry errors. Forms will be developed and data will be stored on a secure site at the Johns Hopkins University biostatistical center. Saliva is collected from the child for cotinine analysis at baseline, 6 and 12 months. Cotinine samples will be analyzed at the Johns Hopkins University Center for Interdisciplinary Salivary Bioscience Research Blood and RAST tests will be collected at baseline and analyzed at the Johns Hopkins Hospital Department of Pathology. (See Letters of Support). Pharmacy data will be collected using our current protocol of obtaining data from all individual and corporate pharmacies listed by the caregiver as used during the prior 12 months for filling child's prescriptions. ^(25, 107) Use of insurance pharmacy and health care utilization data is available for children enrolled in Priority Partners Medicaid HMO, the primary insurer of low-income children attending JHH and other Maryland hospitals. Medical record review will be at baseline, 6 and 12months.

Power Analysis/Sample Size Determination. The study is powered on the difference in the mean number of symptom days in the past two weeks comparing baseline to 6 months follow-up and is based on data in our PAAL study (NR010546). Mean baseline number of symptoms days during the past two weeks was 7.24 (SD 5.31), then decreased to 4.34 (SD 4.69) at 6 months. (Section 2.E.3). Table 3 below provides the number of subjects per treatment group needed to detect a change in the mean number of symptom days from 7.25 at baseline to 4.50, 4.75, 5.25 and 5.50 days, respectively, at 6 months, assuming both an 80% and 90% power, a two-sided t-test and a standard deviation of 4.6 for mean number of symptom days at baseline and 6 months. These sample sizes also assume that the number of symptom days will remain constant over the 6 months among control patients, while those in the intervention group will demonstrate a decrease in the mean number of symptom days over the initial 6 months of the study. The sample size

presented is for each intervention group by age strata (4 groups): AEx age 3-6 yrs, AEx 7-10 yrs, Control 3-6 yrs and Control 7-10 yrs.

Table 3: Power of two-sided level p=0.05 test.

H₀: $u_1 = u_2$ versus H_A: $u_1 \neq u_2$
(u_1 = baseline symptom days last 14 days = 7.25 days)

Power	u_2			
	4.5	4.75	5.25	5.50
90%	59	73	113	147
80%	45	55	85	110

Using the above power calculations, we will need a sample size of 118 per treatment group (accounting for 2 age strata) in order to achieve a power of 90% to detect a 2.5 absolute difference in mean symptom days from baseline (7.25) to 6 months (4.5) for the intervention group. Accounting for a 12% attrition rate, **we plan to enroll 111 subjects per treatment group to achieve a total of 222 subjects**. We expect an effect size of 0.21 (Cohen's $d = 0.43$) for mean number symptom days/2 weeks based on PAAL baseline symptom data. Power estimates were obtained using nQuery Advisor®Release 4.0. ⁽¹¹⁸⁾

Data Analysis for Hypothesis Testing

Preliminary and Descriptive analyses. The data analysis will be performed using an intention-to-treat model. The major independent variable is the AEx Intervention (AEx vs.CON) and primary dependent variable is the number of symptom days and/or nights over past 14 days. Secondary outcomes include number of ED visits and hospitalizations/last 6 months, and number of anti-inflammatory medication refills/12 months, number of school days and work days missed, child asthma control and caregiver quality of life scores. Controller to total medication ratios will be calculated based on 12 month pharmacy records. Initial data analyses will include exploratory inspection using box plots to identify general relationships and potential problems with asymmetry and extreme observations. Both groups (AEx and CON) will be examined for differences in baseline independent/covariate variables i.e. child and maternal age, allergen status. For initial confirmatory analyses, chi-square tests and t-tests will be used for categorical and continuous variables, respectively, in order to examine for statistical relationships between the dependent variables and treatment assignment. The results of these univariate analyses will inform building multivariable regression models that will be created to statistically compare treatment groups for differences in number of symptom days and/or nights, ED visits, hospitalizations and use of appropriate anti-inflammatory medication while controlling for potential confounders including asthma control, allergy status, cotinine level and fidelity of the intervention defined as adherence to AEx visit (yes or no) and number of intervention home visits. A probability level of $p \leq 0.05$ will be considered statistical significance. Procedures for Handling Missing Data. The extent of data missing due to survey non-response will be assessed and if extensive, we will explore using imputation. A principled approach will be conducted if imputation is used, in that a naïve imputation method may distort estimates of standard errors and hypothesis tests. Procedures for multiple comparisons. In order to correct for the multiple comparisons from the large number of proposed t-tests on the same subjects under specific aim 1, we will use the Bonferroni adjustment to preserve the overall type I error for these several tests by dividing the alpha level (e.g. 0.05) by the number of tests proposed. Under specific aim 1, we have pre-selected the following comparisons by intervention group: increased symptom free days and nights (our primary outcome), decreased ED visits, hospital days, missed school and work days, and increased caregiver QOL and child asthma control. We will further adjust the alpha level to accommodate any additional tests that may prove to be clinically relevant under this specific aim.

Analysis by Aim

Aim 1. To reduce asthma morbidity defined as **increase** number of symptom free days and nights (primary outcome), **decrease** missed school days and caregiver work absences due to asthma, ED visits and hospital days and **increase** caregiver quality of life (QOL) and child asthma control. Student's t-test for independent samples will be used to test for group differences (AEx vs. CON) in number of symptom free days and nights, ED and hospital days, school days and caregiver worked days missed and caregiver quality of life scores. These variables will also be examined over time (6 and 12 months follow-up) using appropriate regression modeling techniques for longitudinal data e.g. likelihood methods, mixed models, GEE.⁽¹¹⁹⁾

Aim 2. To improve the use of appropriate anti-inflammatory (controller) medication (receiving ≥ 6 controller medication refills/12 months or achieve a controller-to-total (C-T) medication ratio >0.5) based on

national asthma guidelines.^(8, 111) Student's t-test for independent samples will be used to test for group differences (AEx vs. CON) in the number of anti-inflammatory refills over the 12 month study period. We will also dichotomize the number of anti-inflammatory refills to <6 vs. ≥ 6 refills and C-T ratios < 0.5 versus ≥ 0.5 to test this hypothesis. The anti-inflammatory refill rates also will be examined over time (e.g. at baseline and 12 months) using appropriate regression modeling techniques for longitudinal data e.g. likelihood methods for mixed models, GEE.⁽¹²⁰⁻¹²²⁾

Aim 3. To compare the economic cost and effects of this intervention using a societal and payer perspective cost-benefit analysis as the primary analyses. Means, medians and standard deviations for the total costs including ED visits, hospital days and medication costs, and the value of symptom days will be computed for each group (AEx and CON). Current ED visit costs at Johns Hopkins are: \$1196.49 (Level 4 Professional fee and Hospital costs). Predicted cost of AEx intervention is \$509 (*ED follow-up visit @ \$198 Professional fee and Hospital costs + \$311 home intervention cost*). To make a comparison of costs using bivariate and multivariate parametric techniques, we will conduct analyses that are either non-parametric or that account for the distribution of the data if they are non-normal. Since health care costs are often highly skewed, we expect to use a multivariate approach like the generalized linear model with a log link and the gamma family for the error distribution. Bivariate analyses such as t-tests or analogous non-parametric tests will be performed to examine any differences between the groups. In addition, we will perform multivariate analyses, such as the type described above to control for independent or confounding variables that may modify a relationship between AEx intervention group and health care costs. The cost-saving and cost-effectiveness analyses will combine the medical care cost data described above with the data on the value of missed work days and data on the cost of the intervention. Since data on missed work days and the resources used in the intervention can be linked to individuals, we are able to calculate the total costs associated with care for each child in both groups and the analyses described earlier in the paragraph can be repeated. While it is possible to estimate the difference in costs and to compute a p-value for the difference being different from zero, using parametric techniques we will also bootstrap the results (i.e. take repeated sets of study data observations drawn from the data with replacement) using natural (i.e. non-transformed) dollars.⁽¹²³⁾ The distribution of calculated differences will be used to describe the probability of a cost-savings result. The primary analysis will be a cost-benefit analysis using the societal perspective (including the costs of the intervention, symptom days, and ED visits and hospitalizations) and a cost-benefit analysis from the payer perspective (leaving out the indirect costs of the symptom days). If the AEx intervention is effective and the costs are higher, then it will be necessary to calculate an incremental cost-effectiveness ratio. If not, this secondary analysis does not need to be conducted. The point estimate for the incremental cost-effectiveness ratio is calculated as the difference in the average cost divided by the difference in the average number of symptom free days; this is useful on the assumption that there is a value to symptom free days that is not captured by increased parental productivity. The precision of the ratio can be described using a cost-effectiveness acceptability curve (CEAC) that can be constructed after conducting a probabilistic sensitivity analysis. The bootstrapping technique that will be used will be similar to the bootstrapping technique for the analysis of cost-savings. At the end of each bootstrapping replication, the incremental cost-effectiveness will be calculated. The CEAC uses data from multiple replications and a range of possible values of a symptom free day to summarize data on the probability of having a result that is above or below any given level of cost-effectiveness. The CEAC will be used to infer the likelihood of the ratio being below the \$79.43/symptom free day reported in prior studies.⁽¹²⁴⁾ Two other secondary analyses will include a cost-benefit analysis only from the payer perspective and a cost consequence analysis will describe all the cost components, symptom free days, school and work days missed.

Additional Analyses. Multivariate generalized linear regression models will be used to study the effects of the AEx treatment on child outcome measures while controlling for various independent variables, including both (i) variables hypothesized a priori to predict those outcomes and (ii) covariates found to be significantly associated in bivariate analyses. These models will allow for interaction effects among child characteristics and treatment group and joint analyses of multiple data points (repeated measure for number of symptom days and nights, number of ED and PCP visits). Potential confounding and effect modifying covariates include categorical measures such as child gender and insurance status, caregiver education, and continuous variables of caregiver and child age, caregiver depression and child asthma control level. Complications of the repeated measures design include consideration that repeated measures will be correlated, thus we will use the Generalized Estimating Equations (GEE)⁽¹¹⁹⁾ to provide consistent

estimators of the regression coefficients and their variances under weak assumptions about the actual correlation among a subject's observations.⁽¹¹⁹⁾ These models will express number of symptom days as a function of time, treatment group, and the AEx treatment by time interaction, thus allowing time trends to differ for the different groups. While estimating this mean model, the correlation among multiple observations on the same individual over time will be taken into account. Model-based and robust variance estimates⁽¹¹⁹⁻¹²⁰⁾ will be used as a check on the validity of the longitudinal model. We expect that outcome measures will be influenced by time of year and will control for seasonality by using indicator "month" variables associated with each month that the data are collected. In addition, we will model seasonality using smoothing spline functions to control for potential non-linear effects of time of the year and asthma control. Kaplan-Meier curves for the time to the subsequent ED visit will be calculated for each group. A Cox proportional hazard model will be used to estimate relative rates of return ED visits among the two groups, controlling for baseline characteristics. A log-linear regression will be used to model expected number of visits over 12 months as a function of treatment group and baseline covariates.⁽¹²⁵⁾ In the survival and log-linear regression analyses, standard regression diagnostics will be used to assure assumptions are reasonably satisfied and prevent 1 or a few children from having undue influence on the findings.

Attrition Management/Study Burden. In our current PAAL study, we had a 9% attrition rate at 12 months, but anticipate a 12% attrition rate in the AEx study since families are required to attend a follow-up ED visit. Detailed contact information, names of two individuals who always know caregiver's contact info, will be obtained at recruitment. Participants will be advised that a \$5 gift card incentive is mailed to participant for calling the study office with notification of address change. We have tested the parent questionnaire, obtaining saliva and blood draw during the child's ED visit and 2 month follow-up contact with only two lost to follow-up subjects (2/32, 6%).

Fidelity of Intervention: Video recordings of the first 10 and thereafter 10% of AEx visits will be reviewed by Drs. Butz, Bollinger, Okelo for consistency in the delivery of asthma education, spirometry and ICS prescribing. Drs. Bollinger and Mudd will meet with the AEx PNP monthly for assurance of consistent asthma education delivery. *For the AEx home visits, observation of the first ten AEx home visits and 10% of visits thereafter will be conducted/yearly by Drs. Butz and Kub for consistency of home visits protocol. Any discrepancy between protocol and delivery of intervention will be corrected at time of observation.*

Training of Personnel. All research staff, P.I. and co-investigators received training in Protection of Human Subjects in research studies. Research assistants and interviewing staff will be trained by Dr. Butz on the recruitment and consent protocol, interview surveys and confidentiality of data collection. The AEx-PNP will conduct all AEx clinic visits and certification as an asthma educator is one requirement for employment. The AEx PNP will be trained by Drs. Bollinger, Butz, and Mudd for delivery of the intervention during the AEx visit. Drs. Butz and Kub will train/supervise the CON and the AEx home visiting nurses.

Timeline: The study will require five years (4/01/2013 – 3/31/2018) in order to conduct subject recruitment, intervention delivery, follow-up data collection, and data analysis. See Table 4.

Table 4. Estimated Timeline for Major Activities in AEx Study (April 1, 2013–March 31, 2018)

Potential Limitations with Planned Actions:

A. The intervention may not be generalizable to hospitals serving non-low income populations. While this is a limitation, if effective the intervention could be modified for use in rural and community-based health center because the AEx clinic is staffed by nurse practitioner/nurse, environmental control education can often be referred to local health departments and standardized forms(asthma control, asthma action plans and tests (Spirometry, RAST) are widely available.

B. **Inadequate subject recruitment.** We have had extensive experience with recruiting high risk children with asthma and have an established relationship with Dr. Jean Ogborn, Associate Director of Johns Hopkins Hospital Pediatric ED who serves as co-investigator on the project. If unable to achieve our sample size in the projected time frame, we will seek approval to recruit subjects from additional Baltimore hospitals (Johns Hopkins Bayview Medical Center, University of Maryland Medical System) used in prior studies.

C. Low retention of study participants. Our current Pediatric Asthma Alert study (NR010546) using a comparable population, sustained a 91-95% retention rate at 6 and 12 months. If our retention rate < 80% we will use home visits by experienced RAs, non-intervention staff to track families lost to follow-up.