TITLE: A Patient Advocate to improve real-world asthma management for adults living in the inner-city

A. SPECIFIC AIMS

Asthma, a chronic treatable disease, affects 17.5 million US adults**.** Blacks have 3.3 times the emergency department (ED) visits, 2.2 times the hospitalizations, and 2 times the death rate for asthma compared to whites. Other groups including Puerto Ricans also have increased morbidity. Few interventions have targeted low-income minority adults with moderate or severe asthma and even fewer have focused on the real-world clinical practices where care is provided. Yet, according to an Institute of Medicine report, access to health care and patient-provider communication may be particularly difficult to achieve for low-income and minority patients and contribute to health disparities.[1] We propose to assess the effectiveness, sustainability, and budget impact of a patient navigator intervention to facilitate and maintain patient-provider communication and access to chronic care of moderate or severe asthma in low income minority adults with other chronic morbidities. We will implement the intervention in a variety of clinic practices including those of an urban academic health center, a VA, and a federally qualified health center and in both English-speaking and Spanish-speaking patients. Our intervention is tailored to patients and their clinics, allowing the clinic practice to take account of individual patients' comorbidities and psychosocial and community barriers to accessing care. Informed by focus groups of patients and providers, our intervention activates both groups. It integrates activities with demonstrated efficacy; its feasibility, acceptability, and preliminary efficacy were demonstrated in RC1 HL099612 (HAP Study). Here we test its effectiveness, sustainability, and applicability to the real world.

Our navigator, called a **Patient Advocate (PA)**, according to the preference of patients in the focus groups, works with patients by coaching and modeling preparation for a visit with the asthma doctor, attending the visit with the permission of participant and provider, and confirming understanding of issues discussed. The PA also facilitates scheduling, obtaining insurance coverage, overcoming patients' unique social and administrative barriers to carrying out medical advice, and exchange of information between providers and patients. PA activities are individualized, multi-faceted, take account of comorbidities, and are generalizable to other chronic diseases. The PAs, highly valued by patients in RC1HL099612, are recent college graduates interested in health-related or education careers, research experience, working with patients, and generally have the same race/ethnicity distribution as potential subjects.

This dissemination and implementation project refines the intervention of RC1 HL099612 for real-world practice by 1) conducting a randomized controlled trial that compares the **Patient Advocate Intervention (PAI)** to currently practiced guideline-based usual care; 2) carrying out the intervention in a variety of primary care and asthma specialty practices; 3) extending the observation time to a year to test its sustainability; 4) assessing patient-centered outcomes including asthma control, quality of life, ED visits, and hospitalizations; 5) assessing mediators/moderators of the PAI-asthma outcome relationship; and 6) evaluating its cost-effectiveness.

Aims:

Recruiting 300 adults with moderate or severe persistent asthma from clinics serving low-income, urban, primarily minority patients, we will conduct a **randomized controlled trial (RCT)** to:

Specific Aim 1: Assess whether 6 months of the PAI improves asthma control relative to baseline compared with **usual care (UC)** and whether such a difference is sustained in the 6 months following the intervention's completion.

Specific Aim 2: Assess whether the PAI improves other asthma outcomes (need for prednisone bursts, ED visits, hospitalizations, quality of life, FEV1) relative to baseline compared with UC at 6 months and is sustained in the 6 months following the intervention's completion.

Secondary Aim 1: Evaluate whether improvement in self-efficacy, appointment-keeping, communication with providers, adherence, and navigating ability mediate the effect of the PAI on asthma control.

Secondary Aim 2: Assess whether baseline patient factors (e.g., educational attainment and health literacy, demographics, household income, depression, anxiety, social/community barriers) and provider factors (e.g. demographics, years in practice, primary versus specialty practice), moderate the effect of the PAI on the mediators and asthma control.

Specific Aim 3: Measure the incremental direct and indirect (i.e., productivity) costs of the PAI compared with UC from both payer and societal perspectives and determine the incremental cost-effectiveness of the PAI relative to UC for asthma control and other outcomes.

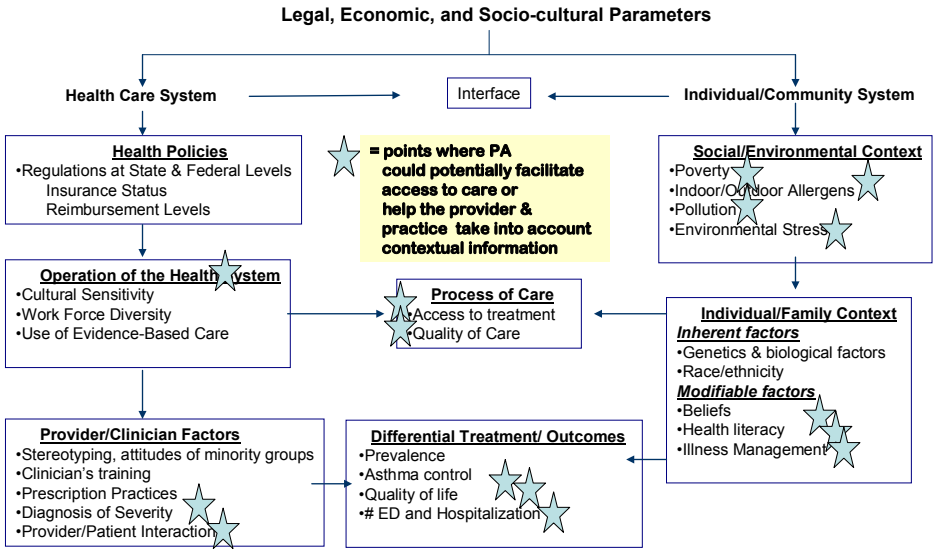
Exploratory Aim: Conduct post-study focus groups of providers to explore awareness of the intervention and response to the PA.

Impact: This proposal is innovative and significant because it 1) compares effectiveness of PA to usual care, 2) focuses on inner-city low-income predominantly minority adults who experience high asthma morbidity, 3) uses a real-world behavioral intervention to test for sustainability in an RCT design, 4) tests a multi-faceted individualized intervention which considers comorbidities as it provides a model of chronic asthma management and is thus generalizable to patients with other chronic diseases and comorbidities, 5) examines patient-provider communication, 6) uses a unique PA, 7) considers both English- and Spanish-speaking patients, and 8) assesses the cost-effectiveness of PAI relative to UC.

B. SIGNIFICANCE

B.1. Asthma, a chronic treatable disease affecting 17.5 million US adults, is characterized by persistent disparity in prevalence, severity, and morbidity.[2-6] Blacks have 3.3 times the ED visits, *2.2* times the hospitalizations, and *2* times the death rate for asthma compared to whites.[2] Puerto Rican populations also have high morbidity.[2, 7] The Institute of Medicine (IOM) found racial and ethnic inequities in health care at two levels: 1) the operation of the practice/health system where administrative tasks are completed; and 2) the individual patient-provider interaction.[1] Asthma provides an excellent setting for addressing both levels. At the practice/health system level features associated with lower quality of asthma care in vulnerable patients include complicated office schedules, insurance, and health forms; lack of evening and urgent visit schedules; and absence of policies that consider cultural or language differences between patients and staff.[8-10] At the patient-provider level, physicians have been found to underestimate asthma severity in black patients.[11] A PA can address both levels in a feasible real-world approach.

Figure 1. Multilevel asthma disparities model by Canino et al [6]



B.2. Canino et al[4] expanded upon the IOM levels, creating a multi-level framework that informs research and practice (Fig. 1). Our PA coaches and models preparation for a visit with the asthma doctor, attending the visit with the permission of participant and provider, and confirming understanding of issues discussed. The PA facilitates scheduling, obtaining insurance coverage, overcoming patients' unique social and administrative barriers to carrying out medical advice, and exchange of information between providers and patients including consideration of patients' environmental and social context. The PAI is individualized, addressing relevant levels of the framework as indicated in Figure 1. Because the PA is a college graduate but not medically trained, PA activities can be distributed within one practice or several for those patients in most need.

B.3. Communication, essential for improving health outcomes and eliminating health disparities, is compromised by language and cultural differences.[1, 4, 12] In addition, accessing care, obtaining insurance, making appointments, and filling forms requires significant literacy. However, half of US adults have no more than basic reading and numerical skills.[13] Health literacy is the subset of literacy skills necessary "to obtain, process and understand basic health information and services needed to make appropriate health decisions",[14] that is, to successfully self-manage a chronic disease like asthma.[14-16] It includes cultural knowledge, reading comprehension, numerical skills, listening and speaking fluency.[14] Low health literacy is found in all patient groups; its prevalence is increased among the poor and underserved minorities and is associated with poorer health access and outcomes, higher health costs, and less patient satisfaction with health providers.[14, 15, 17-28] Low literacy may impair communication, self-efficacy, and ability to navigate the health system.[29-31] In fact, there is concern that the literacy requirements to enroll in health plans under the Patient Protection and Affordable Care Act will impede enrollment by the very groups most in need of its provisions.[32] A PA can address health literacy and cultural context, mitigating health disparities.[29-31]

In asthma, low reading ability has been associated with improper use of inhalers and less asthma knowledge,[33] poor aural skills with poorer disease management.[34] However, inadequate health literacy is not associated with difficulty learning or retaining instructions about medications or inhaler technique,[35] but rather reflects limited access to effective education.[36] Limited literacy is not easily recognized because patients do not disclose such difficulty.[37-39] Screening patients for low literacy may not measure the skills needed for accessing care, but may increase patient anxiety and deter communication.[40] Thus, health literacy experts recommend providing the simplest explanation for all patients, tailoring formats to the individual patient, and confirming understanding using techniques such as "teach-back"(The patient teaches the instructions).[41-43] Our PA promotes practical, immediate and sustainable communication using these methods.

B.4. Inner-city low-income neighborhoods have been called "socially toxic,"[44-46] because the presence of poverty, deprivation, disadvantage, and segregation results in increased exposure to indoor and

outdoor pollutants, inadequate housing, tobacco, and violence. Exposure to violence has been associated with asthma symptoms in children and may be a marker of these toxic exposures.[47-52] The disproportionate psychological stress of living in such communities may explain why interventions at the patient or practice level may not lead to results. Clinicians must understand these stresses and the community resources available to patients. The PA can promote this awareness.

B.5. Patient Navigator activities are efficacious and inform our Patient Advocate Intervention (PAI). Harold P. Freeman, MD proposed the concept of a Patient Navigator (PN) to overcome barriers to early diagnosis and treatment of cancer of patients living in poverty in Harlem.[53-55] In 2005 the National Cancer Center to Reduce Cancer Health Disparities adapted his PN (http://crchd.cancer.gov/pnp/pnrp-index.html). PN-related interventions have focused on uninsured, minority, elderly, and low-income patients in a number of different settings, particularly in screening or assisting with induction of therapy for cancer.[56-58] PNs have arranged transportation, scheduled appointments, ensured medical record availability, and provided social and financial support.[59] PNs have demonstrated efficacy in activities that our PA will accomplish: coordination of care, navigation of the practice, increasing self-efficacy, and facilitating adherence.[56, 60-68] PNs have enhanced communication, fostered trust, and improved patient satisfaction.[64, 69, 70] Interventions that are PN-like also have demonstrated efficacy. Older outpatients accompanied by visit companions who facilitated visit communication at routine medical encounters were more satisfied with their physician.[71] A tailored intervention involving a masters-level social worker working with inner-city children with asthma resulted in reduced asthma symptoms and was most cost-saving in those with more severe asthma.[72, 73] In summary, these efficacious activities are integrated into the PAI which we now implement, testing its effectiveness and cost-effectiveness.

Patient navigators have been nurses,[74] social workers,[72, 73, 75] community health workers[76]; none used the recent college graduates that have been successful in our pilot studies (See D.1.4). Our PAs, accepted by both patients and providers, have demonstrated they can facilitate such communication.[77]

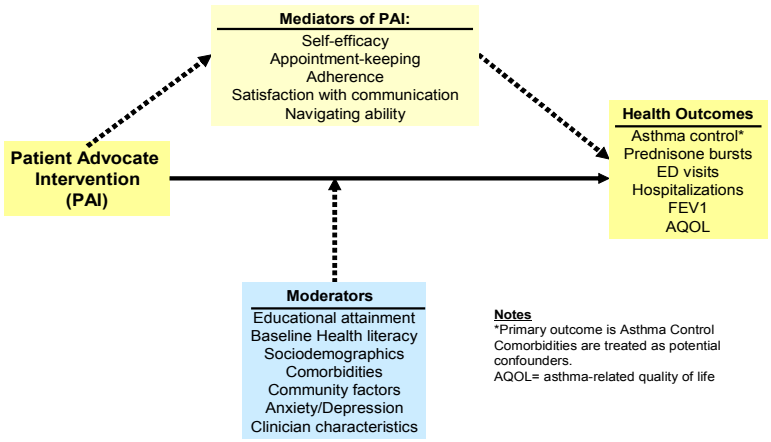
B.6. Comparative effectiveness research (CER) allows dissemination and implementation of a patient-oriented intervention to the real-world.[78-86] CER compares patient-oriented interventions to current care using intention to treat (ITT) analyses in settings representative of "real-world" care.[79] Given the established efficacy of asthma management, CER is needed to assess its real-world effectiveness.[86] CER accommodates demographically diverse patients with complex lives and comorbidities and uses patient-centered outcomes, as in the proposed project. As recommended by a recent NHLBI workshop,[85] stakeholders were engaged in the design of this project through focus groups of patients and providers (D.1.3). Along the multi-faceted continuum from efficacy to CER, our proposal uses a pragmatic trial design,[79, 86] a variety of outcomes important to its stakeholders (patients and providers),[85, 87] and assesses the cost-effectiveness of the intervention in an RCT.[88, 89] Literacy-sensitive disease management and addressing racial and ethnic disparities, themes of our proposal, are advocated as high priority in CER by the IOM and NIH.[90-92]

B.7. Adherence, according to an IOM report,[1] is a measure of the effectiveness of patient-provider communication; poor adherence is hypothesized to be an important mediator of minority status and poorer health and the result of unsatisfactory communication.[1] In asthma, regular use of inhaled corticosteroids, reduces morbidity and mortality,[93-99] and is recommended for all but those with the mildest disease. Poor adherence is presumed to be an important cause of asthma morbidity.[100-103] Underuse occurs in all patient groups,[104] even when medications are provided.[105-108] Reasons include personal-level factors like fear of side effects, not believing in their benefit, or dissatisfaction with medical advice.[108, 109] System-level deterrents include difficulty with access (cost, obtaining refills). Electronically recorded inhaled steroid use is the best measure of adherence in this setting,[105, 110, 111] but is associated with a Hawthorne effect (Change in behavior due to known observation).[77] Additionally, monitoring is not "real-world." Thus, patient-centered outcomes: asthma control, ED visits, hospitalizations will be captured as primary outcomes. Adherence to inhaled steroids, explored as a mediator, will be self-reported, which correlates with monitored adherence.[112] In addition, related to adherence, we will measure keeping of appointments with participant's asthma provider.

B.8. Our Conceptual Model (Fig 2) is based on the multilevel framework of Canino et al[4] (Fig. 1) and hypothesizes that the PAI will improve asthma management measured by patient-centered outcomes: asthma control, prednisone bursts, ED visits, hospitalizations. Within the setting of preparing for, accompanying, and reviewing information and assignments after a medical visit, the PA will improve communication by coaching and modeling ways to ask questions, obtain information, communicate lack of understanding of medical information to providers. We hypothesize as a secondary analysis that the PAI will improve outcomes by improving patient self-efficacy, appointment-keeping, patient satisfaction with communication with the provider, adherence, and navigating ability. The PAI-health outcome relationship may vary depending upon different levels of moderators like educational attainment, and baseline health literacy, sociodemographics, comorbidities, community factors, presence of anxiety of depression, and clinician characteristics.[113] Our model is grounded in Social Cognitive Theory (SCT) that suggests that individuals will engage in a behavior like asthma self-management to the degree they believe that they are capable of carrying it out to achieve a desired result, e.g. improved asthma control.[114-117] SCT proposes that behavior and the environment (e.g. clinical practice, health system, social) interact continuously and these interactions should be taken into

account.[118] The individualized PAI does this. Because implementation of a PAI requires additional resources (time and personnel), we will estimate the incremental cost-effectiveness of the PAI relative to usual care to help ascertain whether the additional resources are partially or completely offset by other savings, such as a reduction in asthma hospitalizations and ED visits.

Figure 2. PAI is a real-world intervention to improve asthma management



C. INNOVATION: Adults with moderate or severe asthma particularly those living in poverty are at risk for poor asthma outcomes. They often have comorbidities and community and social barriers that make accessing healthcare difficult, and frequently have had limited educational opportunities; all of which contribute to difficulties navigating the complicated health system and its practices. In addition, providers with limited time allotted to patients have little opportunity to understand these barriers and patients' priorities. Such patients experience more hospitalizations and ED visits and shorter life spans. The PAI is innovative as a multi-faceted real-world intervention. The PAs, recent college-graduates without specific medical training but representative of the racial/ethnic diversity of the patients, are attractive to patients and the clinical practices alike. Because they do not require medical expertise, their tasks could potentially and ultimately be distributed to several members of one practice or across practices to those patients most in need. The protocol is innovative and significant for 1) focusing on inner-city low-income predominantly minority adults who experience high asthma morbidity, 2) comparing the effectiveness of a PA to usual care in an implementation and dissemination format, 3) using a real-world behavioral intervention tested for sustainability in a RCT design, 4) testing a multi-faceted individualized intervention which considers comorbidities as it provides a model of chronic asthma management and is thus applicable to patients with other chronic diseases and comorbidities, 5) examining patient-provider communication, 6) using a unique PA, 7) using patient-centered outcomes including asthma control and ED visits, 8) carrying out the intervention in a variety of primary care and asthma specialty practices to improve generalizability, 8) includes Spanish- in addition to English-speaking patients, and 9) assessing the cost-effectiveness of PAI relative to UC. By considering mediators, moderators, and cost-effectiveness, we provide a rich implementation design that will inform future comparative effectiveness research of both PAI*s* and other interventions among low-income urban populations.

D. APPROACH

D.1. Two studies, WIN and ongoing HAP, motivate, inform, and support PAI's likelihood of success.[77] These and other studies[30, 52, 105, 108, 119-121] demonstrate our ability to recruit patients from low income urban neighborhoods with moderate or severe asthma and follow them for significant periods of time. All pertain to the patient-MD relationship beginning with a study of adherence which the IOM[1] and our studies found to be a measure of the success of the patient-physician relationship.[105, 108, 109]

D.1.1. WIN Study: "Individualized Interventions to Improve Adherence in Asthma" (R01 HL073932; Apter, PI),[77] a randomized controlled trial (RCT), compared problem-solving (PS) to asthma education (AE) to improve inhaled steroid adherence and asthma outcomes in adults with moderate or severe asthma recruited from clinics serving low-income urban neighborhoods.[52, 77, 121] PS involves identifying specific barriers to adherence, proposing and weighing solutions, trying the best, assessing, and revising. Adherence was monitored electronically.[122] 333 adults (English- or Spanish-speaking) were randomized: 49±14 years, 72% female, 68% African American, 7% Latino, mean FEV1 66%±19%, 52% with ED visits, 31% with hospitalizations for asthma in the prior year. Comorbidities were common: hypertension in 52%, diabetes in 22%, mean BMI 33±9. In an intention to treat (ITT) analysis, there was no difference between groups with respect to overall change in any outcome ($p>0.20$). Mean adherence was 61% ± 27%. Both groups changed similarly from baseline: adherence declined overall by 12% but asthma control,[123] asthma-related quality of life (AQOL), and FEV1 improved overall by 15%, 18%, and 6% respectively. ED visits and hospitalizations did not significantly decrease. While PS was not better than AE, monitoring adherence with provision of medications and attention to patients given to both groups was associated with improvement in some asthma outcomes. Electronic monitoring is not a real-world intervention. Changes in inhaler formulation will make current monitors obsolete. Thus, monitoring is unlikely to be a feasible or cost-effective intervention.

A secondary analysis: Exposure to community violence (ECV).[52] In a longitudinal analysis we asked subjects whether they had witnessed violence in their neighborhood over the 6 months prior to enrollment. ECV was common, occurring in 23% and associated with 2.5 (95%CI: 1.1, 5.6) times more asthma-related hospitalizations, 2.3 (95%CI: 1.3, 3.9) times more ED visits for asthma, 1.7(95%CI: 1.1, 2.6) times more ED

visits for any cause, and lower AQOL (-.40; 95%CI: -.77, -0.025) over the observation period. These results suggest that ECV generates psychosocial distress that directly affects health and/or is a marker for other physical/social exposures that contribute to poor outcomes, like the presence of environmental pollutants, inadequate housing, limited access to pharmacies and grocery stores, and poor public transportation. While a PAI may not be able to remedy these exposures, a PA may facilitate transfer of information so that the clinician can take account of such barriers to asthma management.

Conclusions: The WIN Study demonstrated that an individualized intervention is feasible and acceptable. Monitoring, providing medications, and attention, the intervention in both groups, improved self-management to some degree but ED visits and hospitalizations did not significantly decrease, possibly because these had other determinants from social, community, and health access barriers. WIN did not take account of the practice environment. A real-world individualized intervention is needed that considers the patient, practice, providers, and social and community barriers impeding access to health care.

D.1.2. "Literacy and improving patient-clinician encounters for asthma," (K02 HL088469; Apter, PI), is ongoing research examining whether limited health literacy, particularly numerical skills, hinders patient-physician communication and ultimately the ability to successfully self-manage asthma. We previously developed and validated the Asthma Numeracy Questionnaire (ANQ), a 4-item questionnaire derived from numerical concepts commonly used in patient instructions for self-managing asthma.[119] ANQ scores indicated many adults do not understand the numerical concepts embedded in standard asthma education. Low ANQ scores were associated with hospitalizations and ED visits for asthma.[119] We hypothesized that adequate literacy is associated with better health, mediated by patient-provider communication. We proposed a hierarchical model of numerical and communication skills to guide such communication.[41]

The K02 Specific Aims test in participants of the parent WIN Study whether electronically-monitored inhaled steroid adherence, and asthma outcomes differ by literacy status. To the ongoing WIN Study, we added assessment of numeracy (ANQ) and reading comprehension, the Short Test of Functional Health Literacy in Adults (S-TOFHLA)[124] to baseline questionnaires. In an analysis of the first 80 WIN participants for which we had literacy data, we found only 20% could answer all 4 ANQ items correctly.[30] Less than half understood a question involving percentage (See Appendix, ANQ questionnaire, item 2). However, the reading comprehension score on the Short Test of Functional Health Literacy in Adults (S-TOFHLA)[124] was adequate for 80% of participants. The ANQ results demonstrated that this test can distinguish among literacy levels.[125] Additionally, higher ANQ scores were associated with better AQOL and self-efficacy to accomplish asthma self-management.[30] The association of numeracy and AQOL supports a link between literacy and health.

Preliminary analyses of the entire dataset for this analysis (n=284) adjusting for age, sex, race/ethnicity and the randomized intervention condition of WIN (PS vs AE), found that better adherence was associated with better numeracy (β = 2.70, 95% CI=[0.31, 5.10]) and reading comprehension (β =10.17, 95% CI=[1.48, 18.9]). Similarly, higher AQOL was associated with better numeracy (β =0.14 [0.02, 0.26]) and reading comprehension (β =0.63 [0.18, 1.07]). Asthma control was associated with reading comprehension (β =0.53 [0.18, 0.88]). In summary, these findings support the need for an intervention directed at health literacy and communication as a pragmatic way of overcoming health disparities and improving asthma control.

Conclusions: Numerical concepts in patient education may be difficult for patients to understand. Low literacy, reading and numeracy, is associated with poorer health outcomes. A PAI that facilitates communication with health care personnel about health information may be able to improve asthma outcomes. These preliminary analyses support our proposed secondary aims assessing potential mediators such as self-efficacy and adherence, of the relationship between PA intervention and asthma control.

D.1.3. Focus groups: To develop a feasible acceptable PAI, we conducted 4 focus groups of patients who completed the WIN Study and 2 of providers.[121] Providers and patients thought a PA feasible and potentially beneficial, particularly as a means of social support. Providers thought PAs can help with tasks for which providers are limited by time, staff, or resources, such as helping with obtaining medications, transportation, insurance coverage, and medical information. Patients wanted an advocate (a term they preferred to "navigator"): "someone on your side." They reported being anxious about medical visits, forgetting to ask questions and obtain prescriptions, and forgetting what the doctor said after they left the visit. Patients strongly recommended the PA be like the research coordinator (RC) of the WIN Study who they recognized as an advocate, uniformly preferring an RC to a community PA, possibly because they perceived the RC as accepted by and comfortable with clinical staff. The focus groups revealed that patients experienced a variety of barriers in addition to limited literacy (e.g., transportation difficulties, caring for sick family members, inability to afford co-payments or to obtain insurance), suggesting a resource book (see Appendix) and input from someone familiar with these resources, a PA, would be valuable.

Conclusions: The PAI is acceptable to patients and providers. Patients' need for instrumental social support and providers' need to transmit medical information can be facilitated by the PA.

D.1.4. The ongoing **HAP Study: "A Patient Advocate & Literacy-Based Treatment of Asthma" (RC1 HL099612; Apter, PI)** demonstrates the feasibility of the PAI and compares it to standard asthma education (AE). Participants are adults with moderate or severe asthma (D.3), whose demographics and comorbidities are similar to WIN. Those in the PAI arm work with a non-health-professional PA who assists with and models

preparations for a visit with the asthma doctor; attends visits; and afterwards confirms patient understanding, facilitating scheduling, obtaining insurance coverage, and overcoming other barriers to carrying out medical advice. The PA accompanies participants to 1-3 medical visits as scheduled by their asthma physician during the 16-week participation period. Electronically-monitored inhaled steroid adherence is the primary outcome; asthma outcomes also are obtained. Of 100 participants (100% of planned enrollment) 93 completed the protocol. Of 7 failing to finish, 3 had been assigned to the PAI and 4 to AE. Three withdrew being too busy, with school/job; 4 were lost to follow-up. A PA attended 65 medical appointments. One patient refused to have PA accompaniment to one medical visit. One physician refused to have the PA participate in one patient visit.

Protocol refinements were made. To ensure adequate contact between PA and participant before a medical visit, we added brief PA visits following early data collection visits. Because we found the data collector (DC) received information from participants that might be useful to the PA, we modified the IRB consent to allow the DC and PA to journal about their contacts with participants in a blog accessible only to team members. A resource book of social services was developed. We discovered that we recruited asthmatic adults with high prevalence of low literacy and significant asthma morbidity, high rates of ED visits and hospitalizations. Highly educated patients with demanding highly paid jobs were too busy to enroll.

Preliminary analysis of the 53 PA patients showed improvement in asthma control (decrease asthma control score from 2.23 to 1.67, p= 0.018[126, 127]) and asthma-related quality of life (3.75 to 4.34 p=-.001.[128, 129] (In both, a 0.5 change is clinically significant in an individual). FEV1 improved over 16 weeks from 65% to 69%, p=.25, but not significantly. These statistics provide preliminary evidence of the PAI's efficacy. There was no difference between PA and AE groups, but the comparison was different from what we propose here. In HAP both groups were monitored, supplying a Hawthorne effect, there was not a usual care comparison, the study period was short only 16 weeks, and the study was underpowered for comparisons. Analyzing WIN data during this time, we realized monitored adherence is itself an intervention and so could not be an outcome for the proposed pragmatic intervention. Thus, usual care is a real-world comparison group.

Conclusions: The PAI intervention is acceptable, feasible, and shows evidence of efficacy. HAP and WIN taught us that UC is the appropriate comparison group.[86]

D.2. Methods and Procedures

D.2.1. Summary: This pragmatic RCT will recruit 300 adults with moderate or severe asthma from clinics serving low-income inner-city neighborhoods, randomizing participants 1:1, stratified by practice, to PAI or usual care (UC) for 6 months of intervention followed by 6 months of observation. We will assess PAI's cost-effectiveness. Secondary aims will assess mediators and moderators of the PAI-asthma outcome relationship. We will explore the awareness and response to PAI with post-study focus groups of providers.

D.2.2. Design and Methodological Choices

Design: We choose a **RCT** because randomization reduces the likelihood of bias from both known and unknown confounders.[130] This is particularly important in a study of health behavior where many complex influences are not well understood, but will be equally distributed across comparison groups.

Along the multidimensional continuum of explanatory/efficacy to **pragmatic/effectiveness** designs, this study has strong pragmatic/effectiveness features.[79, 81, 86, 131] These include comparison of the PA intervention to the existing standard of care practiced in both specialty and primary care. The study population enrolled will be demographically diverse with significant asthma morbidity and a range of co-morbidities, selected only on the basis of having moderate/severe asthma (patients with mild asthma do not require the resources of a PAI).[79] Smokers, often excluded in efficacy trials, are included.[86] Randomization should equally distribute smokers, other comorbidities, and relevant characteristics to PA or UC groups. We will recruit from heterogeneous practice settings (primary care, specialty; federally qualified health center, academic health center, Veterans Affairs Medical Center (VA)) and collect a broad range of patient-oriented outcomes: asthma control, ED visits, hospitalizations, prednisone requirements, quality of life.[79, 81] If cost-effective, the intervention can be implemented in a variety of settings.[79] No special strategies will be used to improve study protocol adherence and the protocol is individualized.[79] The analysis is ITT. The NIH and AHRQ have identified both pragmatic designs and achieving health equity as major priorities.[82, 85, 91, 132]

Randomization by participant stratified by practice: The PAI is directed at the patient-PA interaction, so there is little opportunity for the providers to change their behavior with patients not randomized to PA. There has been no evidence of contamination of study arms in HAP. Randomization by clinic requires approximately 20 sites; a multi-site trial is not feasible given the resources. We will convene post-study focus groups of providers to explore their awareness of the intervention and response to it. We will insert a post-study question for all participants (PAI and UC) asking if providers changed behavior during the study.

Eligible consenting patient participants will be randomized 1:1 to PAI or UC. Block randomization with block sizes ranging randomly between 4 and 6 consecutive participants within each site will be employed to ensure that equal numbers of participants are assigned to each of the two groups and are balanced with respect to observed and unmeasured baseline factors.[133] Randomization will be single-blind; study investigators will be blinded to group assignment throughout the study and its analysis. Dr. Morales, the biostatistician, will generate randomization lists based on the above procedure.

Participants are adults recruited from clinics serving low-income neighborhoods. Most asthma studies involve children; adults are relatively understudied. With the WIN and HAP Studies, we established effective recruitment methods and relationships with a variety of clinical practices to recruit and retain adults. Our experience suggests we will recruit patients with significant numbers of hospitalizations and ED visits and other health care costs. An effective intervention will reduce these costs and improve patient health. From HAP, we observed that patients who find a PA most useful will enroll. Very busy, employed, highly educated persons, least likely to benefit from a PA, do not have time to participate and do not enroll.

PA activities: Informed by focus groups (D.1.3)[121] and HAP (D.1.4), the PA will facilitate and model administrative tasks to navigate the health system and practice, prepare for visits, carry out medical recommendations, and overcome social and community barriers to accessing care. The PA will coach patients to articulate appointment goals and concern about or lack of understanding of medical advice. We will individualize PA activities surrounding 1) preparation for asthma doctor visits, 2) medical visits attended by the PA, and 3) ensuring understanding, scheduling, and administrative tasks agreed upon by doctor and patient.[134]

Research coordinators (RCs) will function either as PAs or data collectors (DCs). PAs will not collect data; DCs will not perform PA activities. In our focus groups,[121] patient participants preferred PAs to be like the RCs of the WIN study: recent college graduates interested in health-related or education careers, research experience, further schooling, working with patients, and generally having the same race/ethnicity distribution as potential subjects. We considered other choices: lay health workers, social workers,[75] and nurses; but no one background has been shown to be superior.[135] Ultimately, we followed the recommendation of our focus group participants. End of study questions and comments to DCs and PAs in the HAP study, collected from their blogs, confirmed participants like working with PAs and frequently ask to continue working with them when the study ends. HAP PAs were also well-received by clinic personnel. Since PAs do not take part in medical decision-making, they do not need extensive medical background. RCs will be thoroughly trained in asthma education, research principles, protocol integrity, and cultural competence (D.6.6). Training procedures will be derived from those already developed for the HAP Study.

A resource for accessing social services: The WIN Study and the focus groups underscored the importance of knowledge of resources for overcoming insurance, social, and health system-related barriers. Heather Black, PhD has experience in provision of social services for disadvantaged populations in Philadelphia. She identified resources specific to the needs of asthma patients and developed a resource manual for HAP which we have updated (Appendix). She will review with the PA problems being encountered by participants pertaining to insurance, practice procedures, health system barriers that interfere with patients' communication with their providers and their practices, and self-management of asthma.

Comparison group: UC participants, like intervention participants will receive asthma care from their providers in the participating practices which generally follow asthma guidelines.[103, 136] Data will be collected quarterly (q 3 months) to minimize a Hawthorne effect. We will not provide medications to either group.

The Primary outcome is asthma control, patient-oriented and the primary therapeutic goal emphasized by national and international guidelines for managing asthma[87, 137, 138] and a recent Asthma Outcomes Workshop.[139] Preliminary data from the HAP Study demonstrates overall improvement in asthma control (D.1.4). Other asthma-related patient-oriented outcomes: prednisone bursts, ED visits, hospitalizations, ICU admissions, and quality of life (D.8.1) will be collected.[139, 140]

In WIN and HAP Studies, electronically-monitored adherence to inhaled steroids was the primary outcome. In WIN, both groups improved and the monitoring process was a common intervention between problem-solving and asthma education groups. Monitoring had 3 elements that together improved asthma outcomes: attention, monitoring feedback, and provision of inhaled steroids necessary for electronic monitoring. Thus, although adherence is a measure of patient-provider communication,[1] it is not an appropriate outcome to test the effectiveness of this pragmatic PAI. Additionally, monitored adherence is not patient-oriented or pragmatic. We will measure self-report of adherence, which is correlated to monitored adherence[112] and more pragmatic although less precise (D.8.2).

Mediators and moderators: Potential mediators, testing how the PAI might affect asthma outcomes, were chosen from the literature and our preliminary results (B.8, Fig 2).[113, 141-143] Self-efficacy, a prominent construct in social cognitive theory, is the conviction that one can successfully manage asthma.[114-116] Specifically, we will measure self-efficacy as 1) confidence in filling out medical forms and 2) confidence in adherence to essential inhaled steroid regimens. Appointment-keeping and adherence to inhaled steroid regimens are measures of a working alliance between participant and provider facilitated by the PA. They are manifestations of self-management and should lead to improved asthma outcomes.[144-146] We hypothesize patient satisfaction with communication with providers should improve with the PAI. Finally, we have developed and are validating a questionnaire, Navigating Ability (Appendix) that measures specific participant beliefs and behaviors promoted by the PA. This validation study will be completed before the start of enrollment. Moderators are baseline characteristics that interact with PAI to influence the level of outcomes.[113, 141] We will test whether the relationship between PAI and outcome changes across levels of a moderator,[113, 141] including both patient (baseline health literacy, educational attainment,[30] comorbidities, smoking history, socio-demographics,

community barriers,[47, 52] anxiety,[147, 148] depression[147, 149]) and provider characteristics (demographics, practice type, years in practice).(See D.8.2, D.8.3, D.9)[113]

Duration of patient participation in this pragmatic study is the longest observational period feasible based on HAP/WIN experiences: 12 months. For those in PAI, the intervention will take place in the first 6 months. Both groups will be observed in the second 6 months without intervention. For both groups, number of visits per 12 months with the asthma doctor will be recorded.

Cost-effectiveness analysis: Implementation of a PAI will increase initial resource requirements. However, initial increased resource utilization may be partially or completely offset by savings related to better asthma outcomes, such as reductions in asthma-related hospitalizations and ED visits. Additionally, even if a PAI is not cost-saving, based on analysis of direct medical costs, it may be cost-effective from a societal perspective, which takes into account other non-medical and indirect benefits of improved asthma control, such as increased productivity and self-reported improvement in functional status and quality of life.

Table 1. Data Collection for Specific and Secondary Aims

Measure	Visit 1 Baseline Randomization	Visit 2 Week12	Visit 3 Week 24	Visit 4 Week 36	Visit 5 Week 48
Mediators					
Self-efficacy	x	x	x	x	x
Appointment keeping	x	x	x	x	x
Adherence	x	x	x	x	x
Satisfaction with communication	x	x	x	x	x
Navigating ability	x	x	x	x	x
Moderators					
Educational attainment	x				
Baseline health literacy (ANQ, S-TOFHLA)	x				
Socio-demographics	x				
Comorbidities*					
Community factors (ECV)	x				
Affective State: Anxiety/Depression	x				
Clinician characteristics	x				
Participant Outcomes					
Asthma Control	x	x	x	x	x
Prednisone bursts, ED, hospitalizations	x	x	x	x	x
Asthma–Related Quality of Life (AQOL)	x	x	x	x	x
Spirometry (FEV1, FVC))	x	x	x	x	x

*Comorbidities include diabetes, hypertension, obesity, cancer, smoking history, and other conditions as reported by participant and verified in the medical record.
ANQ= Asthma Numeracy Questionnaire, S-TOHFLA= Short Test of Functional Health Literacy in Adults, ECV= Exposure to community violence.

D.3. Subjects: Inclusion criteria for 300 subjects (1-5 also of the HAP Study) are: 1) ≥ 18 years of age, 2) physician's diagnosis of asthma, 3) prescribed an inhaled-steroid-containing medication for asthma (ensuring the patient is believed to have moderate or severe reversible airways obstruction by their physician), 4) moderate or severe persistent asthma according to the NHLBI Guidelines,[103] 5) evidence of reversible airflow obstruction: (a) forced expiratory volume in 1 second (FEV1) < 80% predicted at the time of screening or within the 3 years prior to this screening, and (b) improvement with bronchodilator: either (i) an increase of ≥15% and 200ml in FEV1 with asthma treatment over the previous 3 years or (ii) after 4 puffs of albuterol by MDI (or 2.5 mg by nebulizer), an increase in FEV1 or FVC ≥12% and 200 ml in FEV1 within 30 minutes,[103, 150] and 6) at least one appointment scheduled with the asthma physician during the 1st 6 months of participation.

Exclusion criteria: 1) Severe psychiatric or cognitive problems (e.g., obvious mania, schizophrenia, significant mental retardation) that make it impossible to understand and carryout PA activities. Formal psychiatric evaluations are outside the scope of this project. However, RCs will be trained to identify patients during screening who do not appear to be mentally competent to carry out study tasks. Individual cases will be reviewed by the PI. In HAP and WIN Studies this has happened in 1-2 instances/study. Each clinical site has mental health facilities for referral of patients. 2) Unable to understand and provide informed consent, 3) Unable to communicate in English or Spanish. 4) Participants of the HAP Study are excluded.

We will not exclude patients with other comorbidities who meet the above inclusion criteria. Patients with comorbidities may benefit most from a PA. Smoking is not an exclusion criterion. Initially, we excluded smokers in WIN, but eliminated this exclusion because it excluded significant numbers of patients, particularly poor patients, who might benefit from the intervention. Although this is a study of asthma patients, the PAI is not necessarily specific to asthma. Thus, defining "pure" asthma, if it were possible, is unnecessary.

D.4. Recruitment sites include primary care and asthma-specialty practices in a variety of settings. There are 2 family medicine, 2 general internal medicine, 2 pulmonary and 1 allergy outpatient practice from the University of Pennsylvania Health System; practices at the Philadelphia Veterans Affairs Medical Center; the community-based primary care practice of the Woodland Avenue Health Clinic, a federally qualified health center; and the Episcopal Hospital Comprehensive Health Center, a primary care practice serving mainly Spanish-speaking patients. All sites have a large pool of patients with asthma and serve urban low income and minority patients from the surrounding communities. We have previously recruited from all sites. Having 10 sites, including both specialty and primary care practices, improves the generalizability of the results by asthma severity and patient demographics and ensures adequate enrollment. Eight sites are within walking distance of our office and the last two are easily accessed by public transportation (See Resources). All participating practices will have an orientation meeting prior to the beginning of recruitment.

D.5. Recruitment procedures: As for the HAP Study, the RC will screen electronic or paper health records for patients with upcoming appointments in participating practices who have an asthma diagnosis and are prescribed an inhaled-steroid-containing medication. Data collectors (DCs) will call or approach potential participants at the practice and request consent for further screening. IRB-approved consent (See Human Subjects) will be read in English or Spanish as appropriate to the potential participant to permit screening. A second consent will be obtained for enrollment. Recruitment will be continuous. Seasonal variation in asthma will be controlled by randomization and by recruiting through all seasons.

D.6. Protocol

D.6.1. Data Collection Visits generally occur at a private location in the practice of the participant's asthma provider. (Most providers are physicians; but some are physician trainees (residents, fellows), or nurse practitioners.) After explanation of the protocol, informed consent is obtained and baseline data collected by the DC (Table 1, Fig. 2)). Participants then are randomized (D.2.2) 1:1 to either PAI or UC. As a pragmatic trial, there is no run-in as this would select those most adherent.[79] Except for the test of reading comprehension, questionnaires are read to patients as they look on in English or Spanish as preferred by the participant. All questionnaires and all scripts have been translated into Spanish and independently reviewed by other native Spanish speakers and compared with English versions. Data collection (Table 1) occurs quarterly. All participants are reminded of data collection appointments with a phone call a few days prior to the visit.

At each visit the DC asks participants how they are feeling and about urgent care obtained since the last visit, e.g., ED visits, hospitalizations, new or increased prednisone prescriptions ("prednisone bursts"). From HAP we know there will be 3-5 participant visits with the clinician during the observation period for both PA and UC participants. PA, but not UC, activities surround these visits. Randomization ensures approximately equal numbers of MD visits (which will be tallied) in participants assigned to PA and UC.

D.6.2. PA protocol: As in HAP, the PA meets the PA-assigned participant after randomization at Visit 1. After introductions, the PA gives the participant some personal background (e.g., where the PA grew up, went to school, career goals) to begin to establish the PA-patient relationship and to motivate the patient to volunteer similar information. The PA gives the participant a notebook containing pages to enter medications; a calendar for appointments; and a page to enter contact information for physicians, pharmacies, and insurance (Appendix). It contains a sample action plan that the PA encourages the patient to discuss with their asthma doctor. This notebook is used at subsequent meetings with the PA and as the patient otherwise desires. At Visit 2 the PA again meets briefly (5 minutes) with the patient following data collection to further solidify the PA-patient relationship. They may review clinician recommendations or converse about personal experiences or plans. In HAP we found it was important for the patient to get to know the PA as much as possible before the medical visits. The PA meets the participant before, during, and after a visit to the asthma-treating clinician and models, facilitates, and empowers patients to complete tasks related to asthma management. Activities before during and after visits were prompted by our focus groups.[121]

A few days <u>before</u> each visit with the asthma clinician: By phone or in person, the PA assists the participant in making a medication list to provide to the MD, if not already made. Patient and PA discuss any problems with obtaining, refilling, or taking medications. The participant reviews any questions she/he plans to address with the clinician, as this has been shown to improve communication and patient satisfaction with the visit.[151] The PA prompts the patient to prepare no more than 2 to 3 points to address at the medical visit (We found preparing too many points to be frustrating to the clinician who may have other issues to discuss and to the patient if they are not addressed). The PA inquires if forms, referrals, or other documents are needed for the visit and helps the patient obtain them if necessary.

The PA meets the patient in the waiting room when the patient comes for a visit. The PA asks the participant if there is an emergency plan for an exacerbation and encourages the participant to discuss this at the visit if it is not well described by the patient. The PA helps the participant organize any needed materials, e.g. study results, medication lists, insurance information in the notebook. The PA uses the waiting time (which is sometimes considerable) to get to know more about the patient's life and priorities.

<u>During</u> the Medical Visit: If participant and clinician permit, the PA accompanies the participant as an observer. In general the PA speaks only if invited by the participant.[121] Patients and clinicians sign consent that allows PAs to take notes to assist with "teach back" (patient repeating provider recommendations).

In primary care practices, other health issues besides asthma will likely be discussed. The PA will assist in organizing the visit to include all health issues and "teach back" to include all health recommendations.

Immediately after the Medical Visit: As needed, the PA facilitates scheduling follow-up appointments with the clinician and/or others as recommended and completion of any paperwork, e.g., insurance forms or other documents. The PA reviews instructions given to the participant at the appointment by asking the patient to "teach back," that is, to teach the instructions as if the patient were the clinician. If the participant has questions for the clinician after reviewing these instructions, the PA and participant complete a report of items needing clarification for the clinician or staff. Such reports have improved asthma outcomes and patient satisfaction.[9] The PA and participant, as necessary, organize medical and administrative information.

Between Visits: If there has been no contact with a participant for a month, the PA calls, and checks how the patient is feeling, general well-being, and whether the patient has sufficient medications. They review upcoming appointments. The PA asks whether there are new problems surrounding obtaining care or obtaining or taking medications and whether there have been ED visits or hospitalizations. The participant with help as needed from the PA, will notify the clinician of problems judged significant by either PA or participant.

The PA will make use of the social service resource book and Dr. Black as needed. With patient consent, PAs and DCs will keep a log of impressions and information given by patients that is shared only among team members. PA visits and the logs will be discussed at weekly team meetings to solve problems patients have in self-managing asthma. (For example, sometimes a patient shares important information with the DC, this mechanism allows the DC to forward it to the PA. If the DC or team is concerned that information impacts on participants' health, the PI will be notified and, as she judges necessary, the medical service).

D.6.3. UC protocol: There are no meetings with a PA; PAs do not accompany participants or play a role in doctor visits. There are phone calls as needed to schedule data collection visits.

D.6.4. Participant honorarium: Potential participants receive $10 for screening. Participants receive a total of $170: $25 for each of data collection Visits 1–4, $70 for completing Visit 5. Public transportation tokens provided for all data collection visits. (No payment is given for PA visits or attending medical visits.)

D.6.5. Participating providers will be informed about the project in a conference and by email prior to enrolling patients. The protocol will be described generally as a study comparing ways to improve asthma outcomes. Clinicians will be asked to complete a brief questionnaire of demographics, type of practice, years in practice, and on strategies used in accommodating patients with low literacy. Since current national guidelines for asthma[87] recommend visits for moderate/severe asthma at 1-6 month intervals if control is not optimal (i.e. symptoms or bronchodilator response), we will ask if we may schedule all otherwise eligible participants for an appointment during study participation, if they had not been seen in the last 3 months and no appointment is scheduled. The HAP Study demonstrated that patients generally have upcoming clinician appointments and there is no difficulty ensuring participants have such a medical visit for asthma scheduled during participation. In that brief 16-week study of 53 patients assigned a PA, 36 patients had at least one visit, 20 had 2 visits, and 9 had 3 visits with their asthma provider.

Upon randomization to PAI, we will send a letter/email to the patient's asthma doctor informing them of the enrollment and briefly describe protocol activities prior to and after a visit. The letter will ask permission, if the participant agrees, for the PA to accompany the participant to an appointment. We will not communicate with doctors of UC participants. Thus, a doctor will likely not know if a patient is enrolled in the UC arm.

D.6.6. RC training and protocol integrity: RCs will train for 3 weeks initially, using procedure manuals of recruitment, protocol, and data collection adopted from HAP. Training topics include asthma pathophysiology and education; spirometry; human subjects research; cultural competence; interpersonal skills; relating to practice personnel; administrative tasks required of patients; procedures for reviewing medical records, screening, enrolling, obtaining consent, recognition of adverse and serious adverse events, and data collection procedures.[152] Training will involve observation of encounters with participants by the project manager and review of procedures and problems at weekly team meetings with the PI. To ensure protocol integrity all sessions will be taped. A random sample of 10% of the sessions will be chosen for formal assessment of integrity by the PI. If a researcher believes a patient's asthma or health is unstable, Dr. Apter and the patient's clinician will be notified immediately. At least two RCs will be fluent in Spanish.

D.7. Post-study focus groups of providers (Exploratory Aim): We will convene three 2-hour focus groups of 5-8 providers, with at least 3 providers whose patient had a PA and some providers who did not come in contact with a PA. Led by Heather Black, PhD, using methodology of our earlier focus groups,[121] providers will be asked about their awareness of and response to PAs and how PAs might change practice procedures. (See Appendix for draft of script). Data will be collected by audio recording and note-takers.

D.8. Measures are classified as predictors (PAI or UC), outcomes, mediators, and moderators (Fig 2, Table 1, **See Appendix for questionnaires**). All questionnaires have Spanish versions.

D.8.1. Outcomes: The primary outcome, asthma control, reflecting symptoms over the past week, will be measured using the 7-item version of the Asthma Control Questionnaire (ACQ).[123, 153, 154] The score is the

the mean of all responses (0=total control, 6=extremely uncontrolled). The minimally important clinical difference is 0.5. A score >1.5 is considered inadequate control.[155] Several other patient-oriented outcomes will be evaluated. AQOL will be measured with the Mini-Asthma Quality of Life Questionnaire (AQLQ).[126, 128, 129] This 15-item questionnaire has a 7-point response scale that provides a mean summary score. A 0.5-unit change is considered clinically meaningful.[129] The AQLQ has been shown to be a useful indicator of AQOL in low-income adults.[156] Participants will report hospitalizations including ICU admissions, ED visits, urgent medical visits (scheduled < 24 hrs in advance), prednisone bursts (a new prescription for ≥ 3 days of prednisone or an increase in an already-prescribed dose for an asthma exacerbation), and other medical visits. DCs will examine medical records for documentation. Spirometry will be obtained using American Thoracic Society procedures for FEV1 and FVC.[150]

Table 2: Project Timeline

Year	1			2			3			4			5		
Months	1-6	7-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36	37-40	41-44	45-48	49-52	53-56	56-60
Start up: finalize IRB approval, finalize CRFs, train staff, create database															
New enrollment		50		100			100			50					
Follow-up															
Data analysis															
Focus groups: set up, conduct, analyze															
DSMB meets	X				X									X	

D.8.2. Mediators explain how the PAI could influence asthma outcomes (B.8, D.2.2).[113] We will measure self-efficacy, appointment keeping, adherence to inhaled steroid regimens, satisfaction with communication with providers and practices, and ability to navigate the clinical practice/health system. Self-efficacy will be measured by response to "How confident are you filling out medical forms by yourself?", a validated question that correlates with REALM, a standard test of literacy.[157, 158] Subjects also will complete our previously validated questionnaire of self-efficacy that asks about confidence to take prescribed inhaled steroids regularly.[105, 108, 159] Appointment-keeping will be assessed by reviewing administrative records to assess if appointments with the asthma provider are kept (appointments kept/appointments scheduled). We will measure adherence to inhaled steroids using the Inhaler Adherence Scale, a 6-item tool which we used in HAP and WIN.[160] Its range is 0-6, a lower score associated with better adherence. In WIN this score correlated with monitored adherence (corr=.23, p=0.002). Patient satisfaction with patient-provider communication will be measured with our previously used 13- item questionnaire.[105, 108] Each item has a 6-point response scale. The sum is used as the measure (alpha 0.74). We are validating a questionnaire, Navigating Ability, which focuses on specific tasks promoted in the PAI protocol (Appendix)**.** The instrument was completed by a small number of patients (n=31); we observed a Cronbach's alpha=0.54, potentially suggesting there are several concepts being measured by the instrument (i.e. multidimensional). We observed a trend towards a positive correlation of the overall score with numeracy (Spearman correlation=0.35, p-value=0.057), reading comprehension (0.30, p=0.098), and perception of benefits over risks of inhaled steroids (0.32, p=0.082).

D.8.3. Moderators are baseline variables, gleaned from the literature, hypothesized to affect the PAI-outcomes relationships.[113] They include patient educational attainment (years of formal education completed), household income, other socio-demographics, comorbidities (patient reported and verified in the medical record including hypertension, diabetes, obesity, cancer, smoking history, etc). Baseline health literacy will be measured with the Asthma Numeracy Questionnaire (ANQ), the brief 4-item questionnaire of numerical concepts (arithmetic, percentage) that we developed and validated.[119] Reading comprehension will be tested using the Short Test of Functional Health Literacy in Adults (S-TOFHLA).[124] Community barriers are estimated by measuring report of exposure to community violence (D.1.1).[52] Social cognitive theory predicts anxiety inhibits learning. We will use the 20 trait items of the State-Trait Anxiety Inventory (C. Spielberger, Mind Garden, Inc).[161] Depressive symptoms will be measured by the Center for Epidemiologic Studies Depression Scale, a validated 20-item scale.[162] Clinician characteristics include demographics, years in practice, type of medical practice (primary care vs. specialty; physician vs. nurse-practitioner; resident vs. attending, etc).

D.8.4. Costs: Direct medical costs of intervention administration will be measured by the resource-costing method.[73, 163, 164] The primary resource used in the treatment intervention is PA time. Each contact, the type of contact, and the duration of the contact (including preparation, travel, waiting and follow-up time) will be recorded by the PA on a case report form initiated at the time of each contact. The cost of a contact per hour is based on PA wage plus a proportion of the fixed costs of training and of the facility. Other medical resources such as office visits, hospital, ED, MD urgent visits will be converted into costs based on insurance reimbursement rates. Drug use is recorded on the case report forms. The cost of medication will be estimated from US average wholesale prices published in the Red Book or actual insurance payments (including patient co-payments).[163, 164] The total direct medical costs of treatment are the sum of all of these components. The perspective for the primary cost analysis will be that of the payer. We also will estimate direct medical costs and incremental cost-effectiveness attributable to the intervention from a societal perspective, including patient co-payments and indirect costs such as patient and family member time, lost/gained productivity etc. The base case analysis will value indirect costs using a standardized representative rate per unit time. Sensitivity analyses will estimate representative wage rates by job category for employed individuals and examine a

range of representative rates for those not employed. We will adjust costs for inflation using the Consumer and Medical Price Indices, as appropriate, and discount costs to the base year using a discount rate of 3%.[163, 164]

D.9. Data Analysis: We will perform descriptive analyses of all variables, then compare PA and UC groups for the adequacy of randomization, examining if covariates or baseline variables including potential moderators of the intervention and mediating relationships are equally distributed among patient groups. These baseline comparisons will be based on t-tests or Wilcoxon rank sum tests for continuous variables depending on the symmetry of the distributions, on logistic regression for binary or ordinal variables; and on Poisson log-linear regression for count data. If imbalances are found at baseline, the relevant variables will be treated as confounders in the ITT analyses and the analyses of mediators and moderators of the intervention on asthma control. To account for the potential for variation in the effectiveness of the intervention across physician practices, our analyses will compensate by including site as a fixed effect in all analyses. Analyses of PA and UC differences with respect to change from baseline at 6 and 12 months for each outcome in Aims 1 and 2 will be based on the ITT principle: all randomized subjects will be included in the analysis regardless of whether they drop out of the intervention or study. We will perform a sensitivity analysis of the missing at random assumption by following Bruce et al[165] with a non-ignorable shared parameter model.[166]

The analysis will be based on random effects (RE) models applied to baseline and all follow-up visits at which outcome data are collected. The RE will be included to account for correlated and missing data. Separate time effects and time-treatment interactions will be specified for each follow-up visit, such that the treatment-time interaction for a particular visit will be the ITT effect on change since baseline. The RE models will be linear, logistic, and log-linear for continuous, binary, and count outcomes, respectively. Similar RE models will be employed for assessment of mediation and moderation in Secondary Aims 1 and 2.

Data description, screening, and reorganization: We will screen data for quality and integrity as proposed by Altman.[167] For all variables we will determine measures of central tendency: mean and standard deviation for continuous variables, median and range for categorical variables. We will examine frequency distribution graphically (histograms, scatter plots) for all variables. Specific concerns will be directed to understanding the pattern of missing values, isolating outliers, confirming the homoscedasticity of observation groups, verifying the coding consistency, examining adherence to normality for variables anticipated to be so, and locating normalizing transformations for continuous variables intended to be investigated as such. For the tools we developed, we will examine internal consistency using Cronbach's α.

Addressing the impact of site on each outcome: First, we will pool participants across sites, assuming no site effect, using logistic and regression modeling to isolate the relationship between outcome and exposure and other demographics. We have stratified randomization to analyze the effect of site. We have amplified the sample size (D.10) to have a large enough sample to conduct this analysis. As a secondary analysis, we will examine treatment-site interactions. In the presence of statistically significant interactions, we will present separate estimates of treatment effects for each site. In the case of statistically, but clinically marginally significant interactions, we will present main effect estimates of treatment effect but with interactions in the model using –1, 0, 1 dummy coding for site, so that the main effects' estimates will be for the average site.

Aims 1 & 2 (To assess whether PAI improves asthma control and other asthma outcomes): The ITT effect of PA relative to UC on change in asthma control and other asthma outcomes since baseline at 6 months will be assessed with estimation and testing of the treatment-6 month visit interaction in the linear RE model (described above) with asthma control as the dependent variable. In addition, the treatment-12 month interaction will be tested and estimated to assess if the ITT effect is retained after the PA intervention ends.

Secondary Aim 1 (Mediators): The mediation analysis will follow the 4-step regression approach for testing mediated effects of Holmbeck.[113] First, we will examine the association between PAI and mediators (D.8.2) by fitting separate longitudinal RE models with each mediator as the dependent variable. These models will test the effects of the PAI relative to the UC group with respect to change since baseline at each follow-up visit for the potential mediators. Second we examine the association between the PAI and asthma control as described in Aim 1. Third, we will assess the relationship between the mediators and asthma control by fitting separate longitudinal RE models with the mediators (D.8.2) as the independent variables and asthma control as the dependent variable. Finally, the mediators with significant effects at steps 1 and 3 will be included as a lagged time-varying covariate in the ITT linear RE model for asthma control in Aim 1. Mediators of the PAI will be assessed by comparing the randomization (intervention) effect estimate with and without the potential mediator in the model. A reduction of at least 15% in the treatment-visit interaction parameters at 6 and 12 months due to the inclusion of the mediator in the model will be the criteria for a significant mediator.[130]

Secondary Aim 2: Moderators of the intervention (D.8.3) will be tested and estimated with 3- and 2-way interactions among the treatment factor, potential moderator, and visit factor in the ITT model in Aim 1. Similarly, moderators of the mediating relationship will be assessed with 3- and 2-way interactions among the treatment factor, mediator, potential moderator, and visit factor in the mediation model in Secondary Aim 1.

Specific Aim 3 (To estimate the incremental costs and incremental cost-effectiveness (ICE) of PA): ICE will be assessed by comparing the incremental cost of PA (including both intervention costs, as well as costs of care) relative to UC per outcome, e.g. cost per day asthma control or avoided ED, hospitalization. The ICE will be determined based on differences in direct costs (payer perspective) and also including indirect

costs (societal perspective) and will be calculated based on differences in mean costs for the UC group from those in the PA group, divided by the mean difference in outcomes (asthma control, prednisone bursts, ED visits, hospitalizations, etc.). We also will calculate the incremental cost per quality adjusted life year as estimated from the AQOL. We will estimate statistical error and construct confidence intervals using bootstrap procedures[168] for the incremental cost difference and the incremental cost-effectiveness ratio (ICER).

Exploratory Aim (Post-study focus groups of providers): Audio records and notes will be coded into categories emerging from the data by independent coders (A Apter, I Bennett, H Black) who will achieve inter-coder reliability.[169] Using the Grounded Theory approach,[170] we will then analyze the agreed upon categories, and place them into themes emerging from discussions.

D.10. Sample size: We will enroll 300 adults (150 per intervention group). The primary outcome (Aim 1) is asthma control at Visit 3 (6 months) and Visit 5 (12 months). While a clinically meaningful difference in asthma control within-individual is 0.5, we expect the average difference across groups to be smaller. The WIN Study demonstrated a small difference in mean change of 0.2±1.1 in asthma control across intervention groups at Visit 8 (6 months).[77] The effect was neither clinically nor statistically significant. A difference in mean change of 0.32 in asthma control was found in a study with a different focus,[171] but the effect was not statistically significant, probably due to the small sample size.

Specific Aim 1: The power analysis is based on the 2-sample t-test with adjustments for 3 or 5 repeated measures per participant. The adjustment for clustering by patient multiplies the estimated sample size under simple random sampling by a design effect, $d=1+\rho(n-1)$, where n=average number of visits per patient, and ρ is the patient intraclass correlation. We apply a conservative intraclass correlation of 0.30. The power analysis also takes into consideration the following factors: 1) 18% drop-out as observed in WIN; 2) adjusted 2-sided significance level of 0.025; and 3) 80% power. With these factors, the study is powered to observe a standardized effect of 0.29 and 0.32 difference in mean change in asthma control across intervention groups at 6 months and 12 months, respectively. **Specific Aim 2:** The power analysis examines the intervention effect on 5 asthma outcome measures at 6 and 12 months. Using the same assumptions but with 2-sided $\alpha=0.005$ to conservatively adjust for multiple comparisons, we will have 80% power to detect a standardized effect of 0.34 and 0.31 between groups at 6 months and 12 months, respectively. **Specific Aim 3:** Power for the economic analysis[172, 173] (costs have greater variability than clinical outcomes) is 81% based on the same effect size, 2-sided α of 0.05, an effect-cost correlation of -0.1, a difference in cost of $500 and a willingness to pay (WTP) threshold of $2500 per year of improved adherence or avoided hospitalization. An increase in the WTP to $3000 results in 98% power. Thus, the sample size will provide sufficient statistical power for assessment of both clinical and economic evaluations (which requires detecting both effect and cost differences).[172, 173]

D.11. Data Management: The Clinical Research Computing Unit will collaborate to finalize CRFs, construct the database, protect its security, perform data entry, review, query and update data; assist with preparation of DSMB reports, and collaborate with biostatisticians as it has for HAP and WIN studies.

D.12. The **Data Safety Monitoring Board** (see Human Subjects) will meet at study start, year 2, and year 5. At these and every 6 months the DSMB will review reports of accrual, baseline comparability between PA and UC groups, adverse events, safety concerns, data quality, maintenance of confidentiality and recommend study modifications and whether the study can continue.

D.13. Timeline is summarized in Table 2. Some staff is already identified and trained. We have established relationships at recruitment sites and successful recruitment strategies. The MOP of HAP needs minor modifications. HAP case report forms require small modifications.

D.14. Anticipated problems: Insuring recruitment/retention: We will use our successful procedures, using electronic medical records, and relationships developed with practices. We obtain contact information, e.g., cell phone, address, for 3 contacts per participant. Incentives will be given for each DC Visit with the largest at the final visit. We flexibly accommodate meeting times for the convenience of participants. RCs will be diverse, reflecting participant demographics. Guaranteeing a culturally appropriate intervention: RCs will undergo formal training. Co-investigators are also diverse and will in observation of the protocol and in staff meetings guarantee a culturally appropriate approach. Standardizing delivery of PA will be accomplished by the use of procedure manuals; standardized, well-annotated, and carefully constructed case report forms; regular direct observation; and audio-taping of researcher interactions with participants. Assuring physicians do not treat UC participants like PA participants: Physicians will not know which of their patients, if any, are enrolled in the UC arm, only those in PA. Almost all of the intervention takes place between PA and patient or is PA-related so it is unlikely to result in change of provider behavior in the absence of a PA. DCs will ask all subjects post-study if they noted changes in their physician over the study period. Post-study focus groups should add support to this claim. Differences in the impact of the intervention between specialty and primary care practices: will be explored in post-intervention focus groups and in the quantitative analysis of outcomes and mediators.

D.15. Summary: This RCT disseminates and implements the PAI to improve asthma outcomes in primary care and specialty practices, in an academic health center, a federally qualified health center, a VA and in English- and Spanish-speaking practices, testing its effectiveness, sustainability, and cost-effectiveness. The real-world individualized PAI is compared to usual care, crafted for a vulnerable population, considers patients' unique contexts, social barriers, and comorbidities and is generalizable to many diseases and medical settings.

References

1. Smedley BD, Stith AY, Nelson AR. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, D.C.: Institute of Medicine. The National Academies Press; 2003.

2. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stat Report 2011:1-14.

3. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma--United States, 1980-2004. MMWR Surveill Summ 2007; 56:1-54.

4. Canino G, McQuaid EL, Rand CS. Addressing asthma health disparities: a multilevel challenge. J Allergy Clin Immunol 2009; 123:1209-17; quiz 18-9.

5. Gupta RS, Carrion-Carire V, Weiss KB. The widening black/white gap in asthma hospitalizations and mortality. J Allergy Clin Immunol 2006; 117:351-8.

6. Ginde AA, Espinola JA, Camargo CA. Improved Trends but Persistent Racial Disparities in Emergency Department Visits for Acute Asthma, 1993-2005. J Allergy Clin Immunol 2008; 122:313-8.

7. Hunninghake GM, Weiss ST, Celedon JC. Asthma in hispanics. Am J Respir Crit Care Med 2006; 173:143-63.

8. Haas JS, Cleary PD, Guadagnoli E, Fanta C, Epstein AM. The impact of socioeconomic status on the intensity of ambulatory treatment and health outcomes after hospital discharge for adults with asthma. J Gen Intern Med 1994; 9:121-6.

9. Lieu TA, Finkelstein JA, Lozano P, Capra AM, Chi FW, Jensvold N, et al. Cultural competence policies and other predictors of asthma care quality for Medicaid-insured children. Pediatrics 2004; 114:e102-10.

10. Lowe RA, Localio AR, Schwarz DF, Williams S, Tuton LW, Maroney S, et al. Association between primary care practice characteristics and emergency department use in a medicaid managed care organization. Med Care 2005; 43:792-800.

11. Okelo SO, Wu AW, Merriman B, Krishnan JA, Diette GB. Are physician estimates of asthma severity less accurate in black than in white patients? J Gen Intern Med 2007; 22:976-81.

12. Diette GB, Rand C. The contributing role of health-care communication to health disparities for minority patients with asthma. Chest 2007; 132:802S-9S.

13. National Assessment of Adult Literacy. Washington, DC: National Center for Education Statistics;Institute of Education Sciences; U.S. Department of Education, 2003.

14. Nielson-Bohlman L, Panzer A, Kindig D, editors. Health Literacy: A Prescription to End Confusion. Washington, D.C.: National Academies Press 2004.

15. Healthy People 2010: Health Communication. Washington, DC: Department of Health and Human Services (http://www.healthypeople.gov/document/html/volume1/11healthcom.htm), accessed 8/17/2010, 2010.

16. Healthy People 2020: Health Communication and Health Information Technology. US Department of Health and Human Services (http://healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=18) (Accessed 6/17/2011), 2011.

17. Health literacy: report of the Council on Scientific Affairs. Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs, American Medical Association. Jama 1999; 281:552-7.

18. Gazmararian JA, Baker DW, Williams MV, Parker RM, Scott TL, Green DC, et al. Health literacy among Medicare enrollees in a managed care organization. Jama 1999; 281:545-51.

19. Baker DW, Parker RM, Williams MV, Clark WS, Nurss J. The relationship of patient reading ability to self-reported health and use of health services. Am J Public Health 1997; 87:1027-30.

20. Weiss BD, Blanchard JS, McGee DL, Hart G, Warren B, Burgoon M, et al. Illiteracy among Medicaid recipients and its relationship to health care costs. J Health Care Poor Underserved 1994; 5:99-111.

21. Ginde AA, Clark S, Goldstein JN, Camargo CA, Jr. Demographic disparities in numeracy among emergency department patients: evidence from two multicenter studies. Patient Educ Couns 2008; 72:350-6.

22. Baker DW, Parker RM, Williams MV, Clark WS. Health literacy and the risk of hospital admission. J Gen Intern Med 1998; 13:791-8.

23. Baker DW, Gazmararian JA, Williams MV, Scott T, Parker RM, Green D, et al. Health literacy and use of outpatient physician services by Medicare managed care enrollees. J Gen Intern Med 2004; 19:215-20.

24. Wolf MS, Knight SJ, Lyons EA, Durazo-Arvizu R, Pickard SA, Arseven A, et al. Literacy, race, and PSA level among low-income men newly diagnosed with prostate cancer. Urology 2006; 68:89-93.

25. Sarkar U, Karter AJ, Liu JY, Moffet HH, Adler NE, Schillinger D. Hypoglycemia is more common among type 2 diabetes patients with limited health literacy: the Diabetes Study of Northern California (DISTANCE). J Gen Intern Med; 25:962-8.

26. Schillinger D, Grumbach K, Piette J, Wang F, Osmond D, Daher C, et al. Association of health literacy with diabetes outcomes. Jama 2002; 288:475-82.

27. Scott TL, Gazmararian JA, Williams MV, Baker DW. Health literacy and preventive health care use among Medicare enrollees in a managed care organization. Med Care 2002; 40:395-404.

28. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med 2011; 155:97-107.

29. Paasche-Orlow MK, Wolf MS. Promoting health literacy research to reduce health disparities. J Health Commun 2010; 15 Suppl 2:34-41.

30. Apter AJ, Wang X, Bogen D, Bennett IM, Jennings RM, Garcia L, et al. Linking numeracy and asthma-related quality of life. Patient Educ Couns 2009; 75:386-91.

31. Bennett IM, Chen J, Soroui JS, White S. The contribution of health literacy to disparities in self-rated health status and preventive health behaviors in older adults. Ann Fam Med 2009; 7:204-11.

32. Martin LT, Parker RM. Insurance Expansion and Health Literacy. Jama 2011.

33. Williams MV, Baker DW, Honig EG, Lee TM, Nowlan A. Inadequate literacy is a barrier to asthma knowledge and self-care. Chest 1998; 114:1008-15.

34. Rosenfeld L, Rudd R, Emmons KM, Acevedo-Garcia D, Martin L, Buka S. Beyond reading alone: The relationship between aural literacy and asthma management. Patient Educ Couns 2010; Epub ahead of print.

35. Paasche-Orlow MK, Riekert KA, Bilderback A, Chanmugam A, Hill P, Rand CS, et al. Tailored education may reduce health literacy disparities in asthma self-management. Am J Respir Crit Care Med 2005; 172:980-6.

36. Weiss BD, Coyne C. Communicating with patients who cannot read. N Engl J Med 1997; 337:272-4.

37. Parikh NS, Parker RM, Nurss JR, Baker DW, Williams MV. Shame and health literacy: the unspoken connection. Patient Educ Couns 1996; 27:33-9.

38. Wolf MS, Williams MV, Parker RM, Parikh NS, Nowlan AW, Baker DW. Patients' shame and attitudes toward discussing the results of literacy screening. J Health Commun 2007; 12:721-32.

39. Wittich AR, Mangan J, Grad R, Wang W, Gerald LB. Pediatric asthma: caregiver health literacy and the clinician's perception. J Asthma 2007; 44:51-5.

40. Davis TC, Williams MV, Marin E, Parker RM, Glass J. Health literacy and cancer communication. CA Cancer J Clin 2002; 52:134-49.

41. Apter AJ, Paasche-Orlow MK, Remillard JT, Bennett IM, Ben-Joseph EP, Batista RM, et al. Numeracy and communication with patients: they are counting on us. J Gen Intern Med 2008; 23:2117-24.

42. Paasche-Orlow MK, Schillinger D, Greene SM, Wagner EH. How health care systems can begin to address the challenge of limited literacy. J Gen Intern Med 2006; 21:884-7.

43. Paasche-Orlow MK, Wolf MS. Evidence does not support clinical screening of literacy. J Gen Intern Med 2008; 23:100-2.

44. Wright RJ. Health effects of socially toxic neighborhoods: the violence and urban asthma paradigm. Clin Chest Med 2006; 27:413-21, v.

45. Wright RJ, Subramanian SV. Advancing a multilevel framework for epidemiologic research on asthma disparities. Chest 2007; 132:757S-69S.

46. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. Am J Respir Crit Care Med; 182:25-33.

47. Wright RJ, Mitchell H, Visness CM, Cohen S, Stout J, Evans R, et al. Community violence and asthma morbidity: the inner-city asthma study. Am J Public Health 2004; 94:625-32.

48. Clougherty JE, Levy JI, Kubzansky LD, Ryan PB, Suglia SF, Canner MJ, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. Environ Health Perspect 2007; 115:1140-6.

49. Berz JB, Carter AS, Wagmiller RL, Horwitz SM, Murdock KK, Briggs-Gowan M. Prevalence and correlates of early onset asthma and wheezing in a healthy birth cohort of 2- to 3-year olds. J Pediatr Psychol 2007; 32:154-66.

50. Swahn MH, Bossarte RM. The associations between victimization, feeling unsafe, and asthma episodes among US high-school students. Am J Public Health 2006; 96:802-4.

51. Cohen RT, Canino GJ, Bird HR, Celedon JC. Violence, abuse, and asthma in Puerto Rican children. Am J Respir Crit Care Med 2008; 178:453-9.

52. Apter AJ, Garcia L, Boyd R, Wang X, Bogen D, Ten Have T. Exposure to Community Violence is Associated with Asthma Hospitalizations and ED Visits. J Allergy Clin Immunol 2010; 126:552-7.

53. Freeman HP. Patient navigation: a community centered approach to reducing cancer mortality. J Cancer Educ 2006; 21:S11-4.

54. Freeman HP, Chu KC. Determinants of cancer disparities: barriers to cancer screening, diagnosis, and treatment. Surg Oncol Clin N Am 2005; 14:655-69, v.

55. Freeman HP. A model patient navigator program. Oncol Issues 2004; 19:44-6.

56. Wells KJ, Battaglia TA, Dudley DJ, Garcia R, Greene A, Calhoun E, et al. Patient navigation: state of the art or is it science? Cancer 2008; 113:1999-2010.

57. Petereit D, Molloy K, Reiner M, Helbig P, Cina K, Miner R, et al. Establishing a patient navigator program to reduce cancer disparities in the American Indian communities of Western South Dakota: initial observations and results. Cancer control : journal of the Moffitt Cancer Center (Cancer Control) 2008; 15:254-9.

58. Jandorf L, Gutierrez Y, Lopez J, Christie J, Itzkowitz SH. Use of a patient navigator to increase colorectal cancer screening in an urban neighborhood health clinic. J Urban Health 2005; 82:216-24.

59. Center to Reduce Cancer Health Disparities Patient Navigator Program, http://crchd.cancer.gov/ accessed 9/27/2010. National Cancer Institute.

60. Fang CY, Ma GX, Tan Y, Chi N. A multifaceted intervention to increase cervical cancer screening among underserved Korean women. Cancer Epidemiol Biomarkers Prev 2007; 16:1298-302.

61. Nash D, Azeez S, Vlahov D, Schori M. Evaluation of an intervention to increase screening colonoscopy in an urban public hospital setting. J Urban Health 2006; 83:231-43.

62. Vourlekis B, Ell K. Best practice case management for improved medical adherence. Soc Work Health Care 2007; 44:161-77.

63. Rahm AK, Sukhanova A, Ellis J, Mouchawar J. Increasing utilization of cancer genetic counseling services using a patient navigator model. J Genet Couns 2007; 16:171-7.

64. Natale-Pereira A, Enard KR, Nevarez L, Jones LA. The role of patient navigators in eliminating health disparities. Cancer 2011; 117:3543-52.

65. Ferrante JM, Chen PH, Kim S. The effect of patient navigation on time to diagnosis, anxiety, and satisfaction in urban minority women with abnormal mammograms: a randomized controlled trial. J Urban Health 2008; 85:114-24.

66. Van Walleghem N, Macdonald CA, Dean HJ. Evaluation of a systems navigator model for transition from pediatric to adult care for young adults with type 1 diabetes. Diabetes Care 2008; 31:1529-30.

67. Szilagyi PG, Humiston SG, Gallivan S, Albertin C, Sandler M, Blumkin A. Effectiveness of a citywide patient immunization navigator program on improving adolescent immunizations and preventive care visit rates. Arch Pediatr Adolesc Med 2011; 165:547-53.

68. Donelan K, Mailhot JR, Dutwin D, Barnicle K, Oo SA, Hobrecker K, et al. Patient perspectives of clinical care and patient navigation in follow-up of abnormal mammography. J Gen Intern Med 2010; 26:116-22.

69. Han HR, Lee H, Kim MT, Kim KB. Tailored lay health worker intervention improves breast cancer screening outcomes in non-adherent Korean-American women. Health Educ Res 2009; 24:318-29.

70. Carroll JK, Humiston SG, Meldrum SC, Salamone CM, Jean-Pierre P, Epstein RM, et al. Patients' experiences with navigation for cancer care. Patient Educ Couns; 80:241-7.

71. Wolff JL, Roter DL. Hidden in plain sight: medical visit companions as a resource for vulnerable older adults. Arch Intern Med 2008; 168:1409-15.

72. Evans R, 3rd, Gergen PJ, Mitchell H, Kattan M, Kercsmar C, Crain E, et al. A randomized clinical trial to reduce asthma morbidity among inner-city children: results of the National Cooperative Inner-City Asthma Study. J Pediatr 1999; 135:332-8.

73. Sullivan SD, Weiss KB, Lynn H, Mitchell H, Kattan M, Gergen PJ, et al. The cost-effectiveness of an inner-city asthma intervention for children. J Allergy Clin Immunol 2002; 110:576-81.

74. Jack BW, Chetty VK, Anthony D, Greenwald JL, Sanchez GM, Johnson AE, et al. A reengineered hospital discharge program to decrease rehospitalization: a randomized trial. Ann Intern Med 2009; 150:178-87.

75. Ferrante JM, Cohen DJ, Crosson JC. Translating the patient navigator approach to meet the needs of primary care. J Am Board Fam Med 2010; 23:736-44.

76. Petereit DG, Molloy K, Reiner ML, Helbig P, Cina K, Miner R, et al. Establishing a patient navigator program to reduce cancer disparities in the American Indian communities of Western South Dakota: initial observations and results. Cancer Control 2008; 15:254-9.

77. Apter AJ, Wang X, Bogen DK, Rand CS, McElligott S, Polsky D, et al. Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: A randomized controlled trial. J Allergy Clin Immunol 2011; 128:516-23.

78. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis 1967; 20:637-48.

79. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. Cmaj 2009; 180:E47-57.

80. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? Thorax 2007; 62:219-23.

81. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003; 290:1624-32.

82. Clancy C, Collins FS. Patient-centered outcomes research institute: the intersection of science and health care. Sci Transl Med 2010; 2:37cm18.

83. Luce BR, Kramer JM, Goodman SN, Connor JT, Tunis S, Whicher D, et al. Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. Ann Intern Med 2009; 151:206-9.

84. Ware JH, Hamel MB. Pragmatic trials--guides to better patient care? N Engl J Med 2011; 364:1685-7.

85. Lieu TA, Au D, Krishnan JA, Moss M, Selker H, Harabin A, et al. Comparative effectiveness research in lung diseases and sleep disorders: recommendations from the National Heart, Lung, and Blood Institute workshop. Am J Respir Crit Care Med 2011; 184:848-56.

86. Krishnan JA, Schatz M, Apter AJ. A call for action: Comparative effectiveness research in asthma. J Allergy Clin Immunol 2011; 127:123-7.

87. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, 2007:NIH Publication 08-5846:1-416.

88. Goss CH. Comparative effectiveness research: what happened to incorporating costs of care? Am J Respir Crit Care Med 2011; 183:973-4.

89. Krishnan JA. Con: comparative effectiveness research. More than dollars and cents. Am J Respir Crit Care Med 2011; 183:975-6.

90. Initial National Priorities for Comparative Effectiveness Research, http://www.iom.edu/~/media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/CER%20report%20brief%2008-13-09.pdf, Accessed 8/31/2010. Institute of Medicine, 2009.

91. Lauer MS, Collins FS. Using science to improve the nation's health system: NIH's commitment to comparative effectiveness research. JAMA 2010; 303:2182-3.

92. Iglehart JK. Prioritizing comparative-effectiveness research--IOM recommendations. N Engl J Med 2009; 361:325-8.

93. Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, Horwitz RI, et al. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. Jama 1992; 268:3462-4.

94. Welch MJ, Levy S, Smith JA, Feiss G, Farrar JR. Dose-ranging study of the clinical efficacy of twice-daily triamcinolone acetonide inhalation aerosol in moderately severe asthma. Chest 1997; 112:597-606.

95. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. JAMA 1997; 277:887-91.

96. Goldman M, Rachmiel M, Gendler L, Katz Y. Decrease in asthma mortality rate in Israel from 1991-1995: is it related to increased use of inhaled corticosteroids? J Allergy Clin Immunol 2000; 105:71-4.

97. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000; 343:332-6.

98. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. J Allergy Clin Immunol 2001; 107:937-44.

99. Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. Respir Med 2002; 96:432-8.

100. Pignone MP, DeWalt DA. Literacy and health outcomes: is adherence the missing link? J Gen Intern Med 2006; 21:896-7.

101. Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute. 1997:Publication 97-4051.

102. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma. National Institutes of Health, National Heart, Lung, and Blood Institute. 2002:02-3659.

103. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report 2007. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute, 2007.

104. Gottlieb DJ, Beiser AS, O'Connor GT. Poverty, race, and medication use are correlates of asthma hospitalization rates. A small area analysis in Boston. Chest 1995; 108:28-35.

105. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids. Socioeconomic and health-belief differences. Am J Respir Crit Care Med 1998; 157:1810-7.

106. Apter AJ, Joffe M, Weber A, George M, Norfleet AL, Cucchiara AJ, et al. Potentially modifiable predictors of adherence with inhaled steroids. Journal of Allergy and Clinical Immunology 2002; 109S:184.

107. Diette GB, Wu AW, Skinner EA, Markson L, Clark RD, McDonald RC, et al. Treatment patterns among adult patients with asthma: factors associated with overuse of inhaled beta-agonists and underuse of inhaled corticosteroids. Arch Intern Med 1999; 159:2697-704.

108. Apter AJ, Boston R, George M, Norfleet A, Tenhave T, Coyne JC, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. J Allergy Clin Immunol 2003; 111:1219-26.

109. George M, Freedman TG, Norfleet AL, Feldman HI, Apter AJ. Qualitative research enhanced understanding of patients' beliefs: results of focus groups with low-income urban African American adults with asthma. J Alllergy Clin Immunol 2003; 111:967-73.

110. Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, et al. Metered-dose inhaler adherence in a clinical trial. Am Rev Respir Dis 1992; 146:1559-64.

111. Riekert KA, Rand CS. Electronic monitoring of medication adherence: when is high-tech best? Clinical Psychology in Medical Settings 2002; 9:25-34.

112. Cohen JL, Mann DM, Wisnivesky JP, Home R, Leventhal H, Musumeci-Szabo TJ, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. Ann Allergy Asthma Immunol 2009; 103:325-31.

113. Holmbeck GN. Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: examples from the child-clinical and pediatric psychology literatures. J Consulting and Clinical Psychology 1997; 65:599-610.

114. McAlister AL, Perry CL, Parcel GS. How individuals, environments, and health behaviors interact. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education: theory, research, and practice, 4th edition. San Francisco, CA: John Wiley & Sons, Inc; 2008. p. 169-88.

115. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 1977; 84:191-215.

116. Bandura A. Self-efficacy mechanism in human agency. American Psychologist 1982; 37:122-47.

117. Bandura A. Self-efficacy in changing societies: Cambridge University Press; 1995.

118. Butterfoss FD, Kegler MC, Francisco VT. Mobilizing Organizations for Health Promotion. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education, Fourth Edition. San Francisco: John Wiley & Sons; 2008. p. 335-57.

119. Apter AJ, Cheng J, Small D, Albert C, Fein DL, Bennett IM, et al. Asthma Numeracy Skill and Health Literacy. J Asthma 2006; 43:705-10.

120. Naimi DR, Freedman TG, Ginsburg KR, Bogen D, Rand CS, Apter AJ. Adolescents and asthma: why bother with our meds? J Allergy Clin Immunol 2009; 123:1335-41.

121. Black HL, Priolo C, Akinyemi D, Gonzalez R, Jackson DS, Garcia L, et al. Clearing clinical barriers: enhancing social support using a patient navigator for asthma care. J Asthma 2010; 47:913-9.

122. Bogen D, Apter AJ. An adherence logger for a dry-powder inhaler: an new device for medical adherence research. J Allergy Clin Immunol 2004; 114:863-8.

123. Juniper EF, O'Byrne PM, Ferrie PJ, King DR, Roberts JN. Measuring asthma control. Clinic questionnaire or daily diary? Am J Respir Crit Care Med 2000; 162:1330-4.

124. Baker DW, Williams MV, Parker RM, Gazmararian JA, Nurss J. Development of a brief test to measure functional health literacy. Patient Educ Couns 1999; 38:33-42.

125. Griffin JM, Partin MR, Noorbaloochi S, Grill JP, Saha S, Snyder A, et al. Variation in estimates of limited health literacy by assessment instruments and non-response bias. J Gen Intern Med 2010; 25:675-81.

126. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest 1999; 115:1265-70.

127. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005; 99:553-8.

128. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999; 14:32-8.

129. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol 1994; 47:81-7.

130. Rothman K, Greenland S. Modern Epidemiology. Philadelphia: Lippincott Williams and Wilkins; 1998.

131. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. J Clin Epidemiol 2009; 62:499-505.

132. National Heart Lung and Blood Institute Advisory Council, http://www.nhlbi.nih.gov/meetings/nhlbac/feb2010sum2.htm#cer. Accessed 8/20/2010. Bethesda, MD: , 2010.

133. Piantadosi S. Clinical Trials: A Methodological Perspective. New York: John Wiley, 1997:276-77.

134. Schillinger D, Hammer H, Wang F, Palacios J, McLean I, Tang A, et al. Seeing in 3-D: examining the reach of diabetes self-management support strategies in a public health care system. Health Educ Behav 2008; 35:664-82.

135. Ramsey S, Whitley E, Mears VW, McKoy JM, Everhart RM, Caswell RJ, et al. Evaluating the cost-effectiveness of cancer patient navigation programs: conceptual and practical issues. Cancer 2009; 115:5394-403.

136. Guidelines Implementation Panel Report for Expert Panel Report 3--Guidelines for the Diagnosis and Management of Asthma; Partners Putting Guidelines into Action. US Department of Health and Human Services, National Institutes of Health, National Heart Lung and Blood Institute, NIH Publication No. 09-6147, 2008:1-45.

137. Global Strategy for Asthma Management and Prevention http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=1561.accessed 7/23/2010. 2009:1-92.

138. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations:

standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180:59-99.

139. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma Oucomes Workshop: Overview. J Allergy Clin Immunol. In press

140. Fulbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Jr., Gern JE, et al. Asthma Outcomes: Exacerbations. J Allergy Clin Immunol. In press.

141. Evans GW, Lepore SJ. Moderating and mediating processes in environment behavior research. In: Moore GT, Marans RW, editors. Advances in environment, behavior and design, Volume 4. New York: Plenum Press; 1997. p. 255-85.

142. Edwards JR, Lambert LS. Methods for integrating moderation and mediation: a general analytical framework using moderated path analysis. Psychol Methods 2007; 12:1-22.

143. Muller D, Judd CM, Yzerbyt VY. When moderation is mediated and mediation is moderated. J Pers Soc Psychol 2005; 89:852-63.

144. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med 2010; 181:566-77.

145. Fuertes JN, Boylan LS, Fontanella JA. Behavioral indices in medical care outcome: the working alliance, adherence, and related factors. J Gen Intern Med 2009; 24:80-5.

146. Fuertes JN, Mislowack A, Bennett J, Paul L, Gilbert TC, Fontan G, et al. The physician-patient working alliance. Patient Educ Couns 2007; 66:29-36.

147. Oraka E, King ME, Callahan DB. Asthma and serious psychological distress: prevalence and risk factors among US adults, 2001-2007. Chest 2010; 137:609-16.

148. Katon WJ, Richardson L, Lozano P, McCauley E. The relationship of asthma and anxiety disorders. Psychosom Med 2004; 66:349-55.

149. Loerbroks A, Apfelbacher CJ, Bosch JA, Sturmer T. Depressive symptoms, social support, and risk of adult asthma in a population-based cohort study. Psychosom Med; 72:309-15.

150. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995; 152:1107-36.

151. Thompson SC, Nanni C, Schwankovsky L. Patient-oriented interventions to improve communication in a medical office visit. Health Psychol 1990; 9:390-404.

152. Calhoun EA, Whitley EM, Esparza A, Ness E, Greene A, Garcia R, et al. A National Patient Navigator Training Program. Health Promot Pract 2008.

153. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14:902-7.

154. Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue beta2-agonist use? Respir Med 2001; 95:319-23.

155. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006; 100:616-21.

156. Leidy NK, Chan KS, Coughlin C. Is the Asthma Quality of Life Questionnaire a Useful Measure for Low-Income Asthmatics? American Journal of Respiratory and Critical Care Medicine 1998; 158:1082-90.

157. Wallace LS, Rogers ES, Roskos SE, Holiday DB, Weiss BD. Brief report: screening items to identify patients with limited health literacy skills. J Gen Intern Med 2006; 21:874-7.

158. Davis TC, Long SW, Jackson RH, Mayeaux EJ, George RB, Murphy PW, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. Fam Med 1993; 25:391-5.

159. Mahony-Anaya P, Wang X, Tenhave T, Frazier C, Jennings R, Mims A, et al. Self-efficacy & Situational Barriers to Adherence in Asthma among Low-Income Populations of Color. Am J Respir Crit Care Med 2007; 175:A547.

160. Dolce JJ, Crisp C, Manzella B, Richards JM, Hardin JM, Bailey WC. Medication adherence patterns in chronic obstructive pulmonary disease. Chest 1991; 99:837-41.

161. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual: State-Trait Anxiety Inventory for Adults. Palo Alto, CA: Consulting Psychologists Press, Inc./Mind Garden, 1983.

162. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement 1977; 1:385-401.

163. Gold MR, Russell LB, Siegel JE, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.

164. Sullivan SD, Liljas B, Buxton M, Lamm CJ, O'Byrne P, Tan WC, et al. Design and analytic considerations in determining the cost-effectiveness of early intervention in asthma from a multinational clinical trial. Control Clin Trials 2001; 22:420-37.

165. Bruce ML, Ten Have TR, Reynolds CF, 3rd, Katz, II, Schulberg HC, Mulsant BH, et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. Jama 2004; 291:1081-91.

166. Ten Have TR, Kunselman AR, Pulkstenis EP, Landis JR. Mixed effects logistic regression models for longitudinal binary response data with informative drop-out. Biometrics 1998; 54:367-83.

167. Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991.

168. Polsky D, Willke RJ, Scott K, Schulman KA, Glick HA. A comparison of scoring weights for the EuroQol derived from patients and the general public. Health Econ 2001; 10:27-37.

169. Krueger RA, Casey MA. Focus Groups: A practical guide for applied research. 3 ed. Thousand Oaks, CA: Sage Publisher; 2000.

170. Strauss A, Corbin J. Basics of Qualitative Research: Grounded Theory, Procedures, and Techniques. Newbury Park, CA: Sage Publications; 1990.

171. Clerisme-Beaty EM, Bartlett SJ, Teague WG, Lima J, Irvin CG, Cohen R, et al. The Madison Avenue effect: how drug presentation style influences adherence and outcome in patients with asthma. J Allergy Clin Immunol 2011; 127:406-11.

172. Glick HA. Sample size and power for cost-effectiveness analysis (part 2): the effect of maximum willingness to pay. Pharmacoeconomics 2011; 29:287-96.

173. Glick HA. Sample size and power for cost-effectiveness analysis (part 1). Pharmacoeconomics 2011; 29:189-98.