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The West Philadelphia asthma care implementation study (NHLBI# U01HL138687)

Tyra Bryant-Stephens MD [a, *], Yolanda Williams [b], Janani Kanagasundaram [b], Andrea Apter [c], Chén C. Kenyon [d], Justine Shults [d]

[a] Community Asthma Prevention Program, Sr Director, Center for Health Equity, Associate Professor of Pediatrics, United States
[b] Children's Hospital of Philadelphia, United States
[c] Perelman School of Medicine at the University of Pennsylvania, United States
[d] Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, United States

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ABSTRACT

Asthma is the most common chronic condition among children, with low-income families living in urban areas experiencing significantly higher rates. Evidence based interventions for asthma are routinely implemented in either the home, school, or primary care setting. However, even when caregivers of poor children are engaged in asthma interventions in one setting, they often have to navigate challenges in another setting, such as an under-resourced home, non-supportive school, or disengaged health care provider. The West Philadelphia Asthma Care Implementation Plan aims to compare the effectiveness of a primary care-based intervention, school-based intervention, and combined primary care and school intervention to usual care for improving asthma control in school-age children to explore if the synergistic effect of Community Health Worker (CHW) support in the home, school, and health care environments will result in improved asthma control. Children ages 5–13 with uncontrolled asthma from four West Philadelphia recruitment sites will be eligible for enrollment. The families of school age children interested in participating will be randomized to receive a primary care CHW or usual care. Those identified as attending a participating school will have a CHW-led school intervention or usual care in school. If proven effective, this care coordination program will assist caregivers in assessing resources, improving self-management skills, and ultimately reducing asthma-related ED visits and hospitalizations as well as provide additional information for healthcare systems and policy makers to inform their decisions about how and where to focus additional resources and investments in childhood asthma care to improve health outcomes.

1. Introduction

Childhood asthma is characterized by prominent, persistent, and pervasive disparities. For instance, in addition to often cited disparities in specific health outcomes and global quality of life [1–4], students with asthma miss three times more school days than students without asthma, with the highest proportion of missed school days in low-income communities [5]. To address asthma disparities in a patient-centered, sustainable manner, and consistent with an ecological framework, one must intervene in all environmental contexts (i.e., home, school, healthcare system, community) of children with asthma. Previous studies demonstrate that community health workers (CHWs) can effectively deliver evidence-based care coordination, environmental mitigation, and asthma education interventions in specific settings [6–8] and that school-based asthma programs support the reduction in absence in an urban setting [9–11]. However, prior CHW interventions for childhood asthma have not been delivered in an integrative manner to connect settings. Utilization of CHWs in a comprehensive community-based intervention to connect home, school, healthcare system, and community for school-aged asthmatic children and their caregivers may be an important step in eliminating asthma outcome disparities.

Keywords: : CHW, Community Health Worker; ED, emergency department; CAPP, Communitiy Asthma Prevention Program; WEPACC, West Philadelphia Asthma Care Collaborative; EBI, Evidence-based intervention; SBAT, School-based Asthma Therapy; CHOP, Children's Hospital of Philadelphia; pCHW, primary care community health worker; sCHW, school-based community health worker; IRB, institutional review board; OAS, Open Airways for Schools; SAMPRO, School-based Asthma Management Program; ACQ, Asthma Control Questionnaire; EHR, electronic health record

* Corresponding author.
E-mail address: stephenst@chop.edu (T. Bryant-Stephens).

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The potential synergistic strength of integrating interventions across multiple sectors (home, school, community, healthcare system) has not been fully leveraged despite knowledge that multi-level interventions are most effective [12]. Currently evidence-based interventions (EBI) for asthma are routinely implemented in either the home, school, or primary care setting. Prior studies have shown that the school environment is an effective place to deliver self-management interventions for children with asthma leading to reduced healthcare utilizations [13,14].

Even when caregivers of poor children are engaged in asthma interventions in one setting, they often have to navigate challenges in another setting, such as an under-resourced home, non-supportive school, or disengaged health care provider. In one study a comprehensive school management program to promote care coordination and better asthma management conducted by school nurses did not succeed because it placed additional responsibilities on the school nurse and there was no buy-in from the primary care practice [15]. CHWs providing the connection between the home, school, and primary care practice may reduce the burden on providers and caregivers and facilitate asthma management for school-aged children. Further, CHWs, as community residents, are knowledgeable about the public school system and can help parents connect to local resources. CHWs may provide the missing link to coordinate between multiple sectors to optimize interventions [16].

The Community Asthma Prevention Program (CAPP) has a two decade history of utilizing CHWs to improve asthma outcomes of children in Philadelphia [17,18]. Residents of inner-city Philadelphia have been trained and employed as CHWs to effectively provide home asthma education and environmental mitigation for children who have asthma-related ED or hospital visits. Building on this foundation, we established a network of stakeholders, the West Philadelphia Asthma Care Collaborative (WEPACC), with representation from public housing, healthcare (providers and payers), community (organizations and caregivers), and schools. As a result of a local needs assessment, resource mapping, and months of planning, we designed an asthma care implementation program with the broad objective of integrating home, school, healthcare system, and community for school-aged asthmatic children in West Philadelphia using CHWs to deliver sustainable patient-centered evidence-based interventions. The evidence-based interventions include (1) a primary care-based Yes We Can™ Children's Asthma Program with home visitation, (2) a comprehensive and rigorously evaluated school-based intervention, Open Airways For Schools®, and (3) School Based Asthma Therapy [19–21]. CHWs will function as the hub of each intervention, serving either as primary care CHWs or school CHWs to provide a network of education, care coordination support, and to facilitate communication for families of children with asthma between the four sectors.

1.1. Objectives and hypothesis

The primary aim of the West Philadelphia Asthma Care Implementation Plan is to compare effectiveness of a primary care-based intervention, school-based intervention, and combined primary care and school intervention to usual care for improving asthma control in school-age children. Interventions in the home, school and primary care environments will utilize the community health worker (CHW) model. The secondary aim of this study is to explore the moderators and mechanisms of effectiveness of the interventions. Our hypothesis is that the synergistic effect of CHW support in the home, school, and health care environments will result in improved asthma control.

2. Methods

2.1. Study setting/participants

Philadelphia is often cited as the poorest big city in America [22]. With currently 23.3% of residents living beneath the poverty line, Philadelphia easily ranks in the top three largest U.S. cities with the highest rate of poverty. The West Philadelphia Asthma Care Implementation Plan serves residents of West Philadelphia where poverty rate is even greater, at thirty to forty-five percent in some areas [22]. The population of West Philadelphia is primary African American.

The West Philadelphia Asthma Care Collaborative (WEPACC) along with the investigators informed the design of this study [59]. WEPACC is a multi-stakeholder group which includes representatives from the community, school districts, parents, managed care organizations, public health department and primary care providers. The investigator group includes a parent co-investigator who resides in West Philadelphia and participated in all investigator activities. The West Philadelphia Asthma Care Collaborative continues to meet bimonthly to review progress, troubleshoot implementation issues and plan for sustainment. Our stakeholders provide insight regarding their needs to support this project long term and if our outcomes are favorable, we believe that we have the important stakeholders at the table to sustain this intervention.

Children with asthma are recruited from three Children's Hospital of Philadelphia (CHOP) primary care sites located in and around West Philadelphia neighborhoods, as well as at CHOP's emergency department and the West Philadelphia office of the Pediatric and Adolescent Medicine Centers of Philadelphia (see Fig. 1).

For the school intervention, School District of Philadelphia public elementary schools in West Philadelphia will be invited to participate in the study. Several public charter elementary schools in West Philadelphia will also be invited to participate, some of which are served by school-based health centers. In total no more than 36 elementary schools will be invited to participate as a school partner in the West Philadelphia Asthma Care Implementation Plan. This study was approved by the Children's Hospital of Philadelphia Research Institute. The study started recruitment in May 2018 and completed enrollment in June 2021 (Fig. 2).

2.2. Study design

A factorial design will be implemented to evaluate the effectiveness of the following primary care and school evidence-based interventions (EBIs): (1) Yes We Can™ Children's Asthma Program in primary care and home settings, (2) Open Airways For Schools® and (3) school-based asthma therapy (SBAT) in the school environment. The families of school age children living in West Philadelphia with uncontrolled asthma will be recruited and those interested in participating will be randomized to receive a primary care CHW (P+) or usual care (P-).Those identified as attending a participating school will have a CHW-led school intervention (S+) or usual care in school (S-). All study partner schools will be randomized to receive a school CHW or to continue with usual asthma care in school. Children who do not attend a participating school (S^0) will be randomized to receive a primary care CHW (P+) or usual care (P-) and no school data is expected for these participants (Fig. 1).

Table 1 describes the proposed 2-by-2 factorial design, which is partly clustered (by school) and results in six treatment groups. The cells A, B, C, D will permit comparison of any of the 3 combinations of school and child intervention (A, B, C) against the group that has neither (D). At the same time, it will permit marginal analysis of the effect of the school intervention (A + B vs C + D), and the marginal effect of the navigator intervention (A + C + E vs B + D + F). For each of the cells of interest, we collect baseline data on children and then fol-

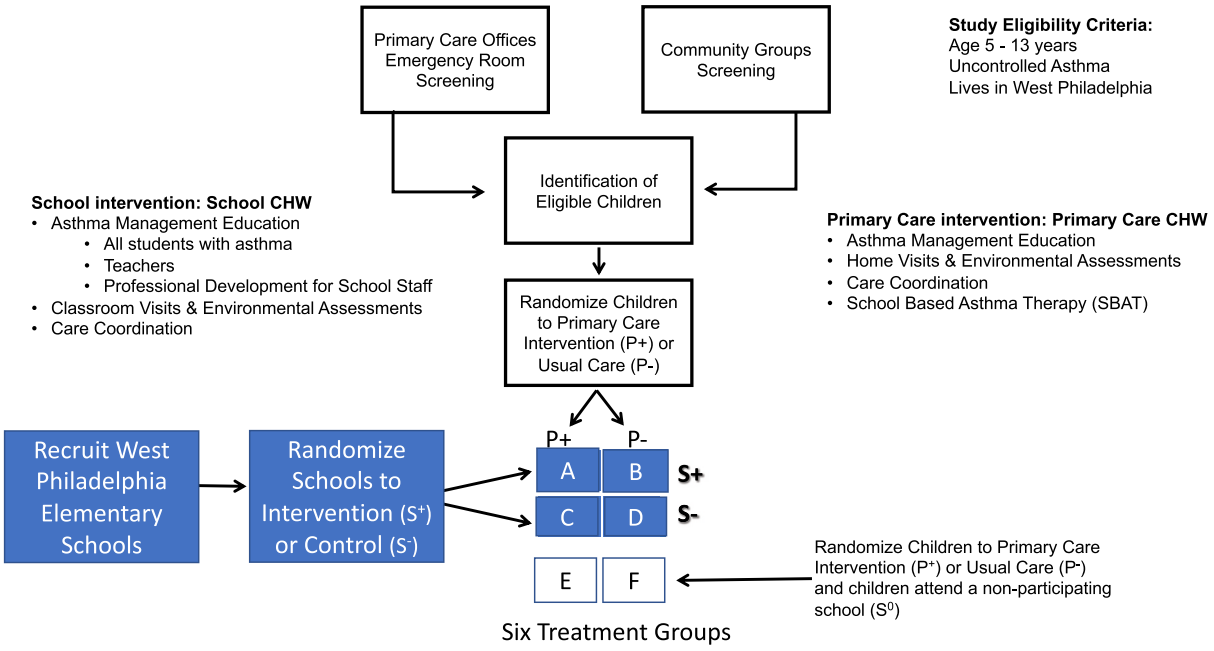

Fig. 1. Wepacc study design.

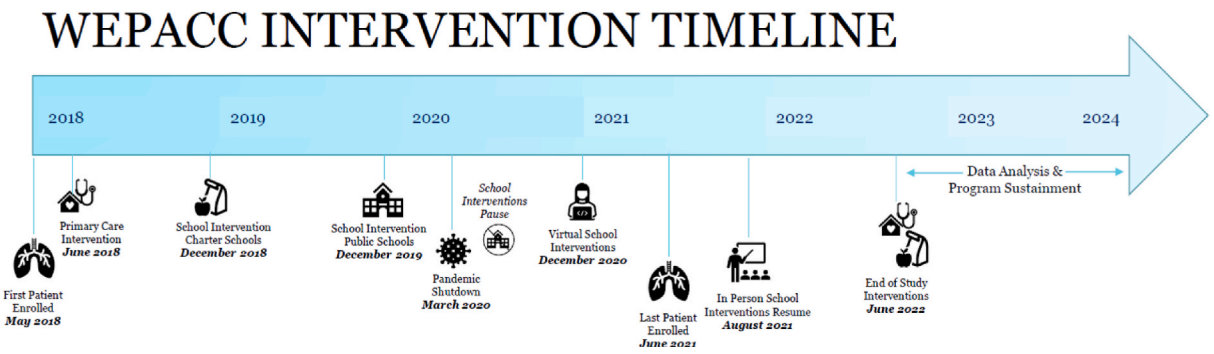

Fig. 2. Intervention timeline.

Table 1
Factorial design by child and school level interactions

		Child-Level Intervention	
		P^+	P^-
School-Level Intervention	S^+	A	B
	S^-	**C**	**D**
Non-Participating Schools	S^0	**E**	**F**

low schools and children over time. This design avoids contamination and interference through cluster randomization at the clinic-level, but benefits from added power of a longitudinal analysis. The factorial layout permits estimation (and testing) of interaction between the school and individual interventions. It also allows for use of data from children who are from nonparticipating schools (groups E and F).

2.3. Randomization

The overall design has stratified participating schools into at least five groups to enhance balance at baseline in school characteristics (size, location, charter status). Randomization of schools to the school-level intervention (S+) or none (S-) will be stratified by these predefined groups. Asthma patients and their families will be recruited in primary care and after consenting to participation will be randomized to receive a primary care CHW (child-level intervention) (P+) or usual care (P-), and these randomizations will be stratified by school and clinic of recruitment. Allocation concealment will be preserved by randomly permuted block, and this approach will also preserve balance of intervention arms within schools over time. Randomization at the child level will proceed using randomly permuted blocks with varying block sizes. Details about the implementation of the randomization are provided in Appendix A.

2.4. Eligibility criteria

Children ages 5–13 years old who reside in West Philadelphia (zip codes 19104, 19131, 19139, 19142, 19143, 19151, or 19153) who have been diagnosed with asthma and have had at least one systemic steroid course administered for an asthma flare in primary care, the ED, or an inpatient setting within the previous 12 months will be eligible for enrollment. Children must also receive primary care at one of the four study recruitment sites to meet study eligibility criteria.

2.5. Screening and recruitment

We will screen electronic health records to enroll 600 children who are residents of West Philadelphia with uncontrolled asthma. Additionally, the CHOP Emergency Department (ED) will screen and refer eligible children for enrollment.

Participants that meet eligibility criteria will be provided information about the study and invited to participate. Caregivers will complete an informed consent document that has been reviewed and approved by the CHOP IRB prior to study participation. Caregivers will be given sufficient time to review the informed consent document, ask questions and decide whether to consent to participation in the study.

2.6. Primary care-based intervention

Children who are randomized to the child-level intervention (P^+, Groups A, C and E) will be assigned a primary care community health worker (pCHW). We will implement the *Yes We Can*™ Children's Asthma Program [20] intervention which is a medical-social model based on a chronic care approach, including risk stratification, clinical care management, social care coordination by a community health worker, and primary care provider asthma champions. This intervention includes asthma education and trigger reduction home visits and care coordination. There will be four home visits over 12 months implemented by the pCHW, integrated into the primary care practice.

The pCHW will accompany the caregiver to the child's primary care appointments and conduct in-office asthma teaching on asthma medications, devices and updates to the asthma care plan as needed. The pCHW will also assist caregivers in voicing questions or concerns to the primary care provider regarding the child's asthma medications or treatment plan. The family's assigned primary care CHW will schedule patients for follow-up visits with the primary care provider and coordinate specialist visits as needed. Study visits at 3, 6, and 9 months may be scheduled during routine asthma follow-up primary care visits. A member of the research team other than the assigned pCHW will administer study questionnaires at these visits. We will hire four pCHWs for this intervention.

Home Visits 1, 2 and 3: Three home visits will occur within the first two months after enrollment. The pCHW will assist the caregiver in choosing up to three care coordination goals such as keeping child's asthma care appointments, reducing secondhand smoke exposure and administering asthma medications properly. These goals will be assessed with the caregiver throughout the year. At the first visit the pCHW will conduct a detailed environmental assessment of the living area and child's bedroom for common asthma triggers. Based on those findings the pCHW will educate caregivers regarding asthma trigger avoidance and provide supplies to reduce asthma triggers. These supplies include a mattress and pillow cover, roach bait, mousetraps, HEPA-filter vacuum cleaner, adhesive floor tiles (after removal of carpet), and other trigger reduction supplies. At subsequent visits the pCHW will conduct a brief environmental assessment of the living area and child's bedroom. The pCHW will also note medications and dose counter number for each asthma medication prescribed to the enrolled child. The pCHW will review with the caregiver the proper medication administration techniques for use of asthma medications and devices.

For home visits that cannot be conducted in person due to health or safety concerns, video conferencing through a HIPAA-compliant application licensed by CHOP will be utilized. In this event, asthma trigger reduction supplies will be provided to families via U.S. postal mail or by home drop-off with caregivers providing confirmation of receipt.

Home Visit 4 will take place at 12 months post-randomization, the pCHW will conduct an environmental assessment to document trigger reduction techniques utilized in the home.

2.7. School-based intervention

Twenty-eight elementary schools in targeted zip codes were identified by the School District of Philadelphia to participate in this study. In addition, eight public charter schools committed to participate. Half of the schools (S^+) are randomized to receive Open Airways for Schools *Plus* designed by Clark et al. an asthma education and care coordination EBI for schools and School Based Asthma Therapy (directly observed controller medication use) [19]. In years 5 and 6 of the project the remaining schools (S-) will receive training on how to implement the evidence-based programs.

West Philadelphia elementary schools who have agreed to participate will be randomized to either receive the school intervention facilitated by a school CHW (sCHW) or usual school care. The school intervention will include: (1) Open Airways for Schools® curriculum for all children with asthma, (2) Orientation to asthma and control strategies for principals and school personnel at the start of each school year led by the study team along with the sCHW, (3) For School District of Philadelphia public schools, walk-throughs for custodial personnel to address potential environmental asthma triggers. This will be managed and conducted by school district personnel, and (4) Assistance with obtaining asthma care plans and medication administration forms for students randomized to receive a primary care community health worker (pCHW). This will be facilitated by the sCHW. Open Airways for Schools (OAS) *Plus* designed by Clark [14] et al. seeks to improve the disease management skills of children with asthma and enhance control of asthma in school [14]. This EBI contains four "essential components" of the recently published School-based Asthma Management Program (SAMPRO) summit guidelines and has been found to decrease both asthma symptom days and school absences [23–25]. One OAS class series will be conducted by the sCHW each semester. We will hire four SCHWs for the school interventions.

For participants assigned to both interventions (P^+S^+ or Group A), the sCHWs and pCHWs will coordinate care across the school nurse and primary care offices. In addition to the primary care and school interventions above, this treatment group will receive enhanced care coordination with School-Based Asthma Therapy (SBAT) for prescribed daily controller medication [26]. The pCHW will obtain a copy of the current asthma care plan, school medication administration form, a rescue inhaler prescription for school, and an asthma controller medication prescription to conduct school-based asthma therapy. For many participants, asthma medications and devices for use at school will be delivered to the school nurse by a local pharmacy. Primary Care CHWs will obtain a current asthma care plan and medication administration form for each participating student and transfer these documents directly to sCHWs at weekly study team meetings. The school CHW will then hand deliver these items to the school nurse office to include with the student's school health records. The school nurse and sCHW will coordinate with teachers to schedule an SBAT intake appointment for students eligible to participate in school-based asthma therapy and also schedule a time for the child to return to the office for daily medication administration. During the intake appointment the school nurse will assess the ability of the student to self-administer. For students not cleared to self-administer, the school nurse or his/her designee will administer the daily asthma controller medication. Asthma medication use (both rescue and controller) will be documented by the school nurse and sCHW [26]. If nurse is not present, as per school protocol, the principal will be responsible for assigning oversight of this task. Students eligible for SBAT have been randomized to receive a primary care CHW, therefore asthma management skills will be reinforced at home, school and in the primary care office for these participants.

2.8. Non-intervention schools (usual school asthma care)

Participating schools randomized to continue usual school asthma care (S^- or Groups C and D) will be offered training after the study's data collection period has ended and during the last year of grant funding in how to implement the school asthma interventions. Schools will also be provided with information on how to sustain the program through managed healthcare organization reimbursement for sCHW services.

2.9. Usual care or control group

Families of children randomized to receive usual primary care management for asthma, and whose children do not attend a school randomized to receive the school intervention (Groups D and F), will be offered Community Asthma Prevention Program (CAPP) asthma classes conducted at community sites. Registration is free for CAPP asthma classes and the course series, when offered, is available to all in the community.

2.10. Study visits

After study enrollment baseline study data (questionnaires) will be collected and pulmonary function testing will be administered. Study data will also be collected at 3, 6, and 9 months after enrollment. At 12 months a primary care office visit will be scheduled, pulmonary function testing (spirometry) administered and end-of-study data collected.

For families randomized to receive a primary care CHW, a caregiver survey evaluating satisfaction with the assigned primary care community health worker will be administered via telephone between 13 and 24 months post-randomization and after all outstanding primary care and school interventions have been completed. Families randomized to receive usual primary care will have the opportunity to receive one home visit by a pCHW for an asthma trigger home assessment and to receive asthma trigger reduction supplies.

2.11. Subject withdrawal

Participants may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study procedures. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject has completed or withdrawn from the study, these events will be recorded in the source documents and on the CRF. The IRB and the study sponsor will also be notified immediately. If a participant withdraws prior to completing the study, all previously collected data will be stored and used for analysis.

2.12. Outcomes

The primary outcome, asthma control, will be measured using Juniper's Asthma Control Questionnaire (ACQ), a validated instrument for children and adults [27]. The ACQ will be administered to the caregiver at baseline, 3 months, 6 months, 9 months, and 12 months post-enrollment.

Secondary outcomes include symptom-free days, school absences, and healthcare utilization. Symptom-free days will be collected by caregiver recall of the previous two weeks, consistent with previous studies [28,29]. School absences will be collected directly from the school and by caregiver report. Asthma-related emergency department and inpatient visits at CHOP will be obtained through CHOP's electronic health record (EHR), and Cost-savings will be analyzed through a cost analysis survey administered to caregivers at baseline and 3, 6, 9 and 12 months post-enrollment (Table 1b).

Table B1 in Online Appendix B describes the study outcomes and planned timing of measurements.

Table 1b
Study outcomes.

Primary	Secondary	Implementation
Asthma Control (ACQ)	Inpatient Visits Emergency Visits School Absenteeism Cost Savings	Fidelity Adoption Sustainability

Data will be collected for all individually randomized participants at baseline, 3, 6, 9 and 12 months by a member of the research team. Participants will receive $25 for a completed baseline, 3, 6, and 9 month data collection study visit and $45 for the end of study data collection visit at 12 months.

2.13. Additional individual participant measures

- Enrolled children will be measured for height and weight using standard scales and stadiometers at baseline, and 3, 6, 9, and 12 months following enrollment. If not completed at a study visit, this data will be collected from the EHR.
- Pulmonary function testing (spirometry) will be collected from the EHR. Trained study staff will conduct pulmonary function testing for participants at baseline, 3, 6, 9, and 12 months post-enrollment if not completed as part of routine clinical care. If possible, spirometry results will be printed and stored in the child's research study chart. Pulmonary function testing completed for clinical purposes within one month before or after a study visit will be collected from the EHR if testing is not completed at the time of a study visit.
- For participants receiving the primary care intervention, CAPP's asthma knowledge survey will be administered at select home visits to assess caregiver knowledge before, during and after the primary care intervention.
- The Caregiver Needs Assessment will be administered to the parent/caregiver at the baseline visit. The needs assessment is a validated instrument that focuses on the caregiver's knowledge about asthma avoidance measures and their comfort level with managing their child's asthma. For participants receiving the primary care intervention, this tool will assist the primary care community health worker with tailoring the educational component of the program to fit the needs of the individual family.
- Tracking forms will be utilized to document time, date, and dose of controller medication administered for eligible School-Based Asthma Therapy participants.
- A classroom environmental assessment for each student enrolled in the study and attending an intervention school will be conducted by the school CHW at baseline and at the end of the school semester for enrolled students.

2.14. Group level school measure

- As part of the Open Airways for Schools Curriculum, a pre- and post-test will be administered.

Moderator variables will be measured using the Child Asthma Risk Assessment Tool (CARAT) designed to help clinicians, asthma counselors and parents determine potential risks for children with asthma [30,31].

Fidelity to the school EBI's will be monitored via observation by study staff utilizing yes/no completion checklists of core components of each intervention. It is expected that 90% of the core components will be implemented for maintenance of fidelity to the intervention.

2.15. Statistical considerations and power

2.15.1. Overview of statistical approach

The primary analysis will be based on an intention to treat approach, so that all subjects will be analyzed according to the group to which they were randomized at Study Visit 1. Reporting will follow the CONSORT guidelines for randomized studies and cluster randomized designs.

2.15.2. Baseline data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). We shall first examine balance across the 4 treatment groups in the child-level characteristics (Table C1 of Online Appendix C). To that end, we shall use conventional balancing diagnostics, such as comparisons of percentages of patients by categorical factors and by standardized differences for continuous factors, and/or comparisons of distributions. All will be supplemented by graphical display. These diagnostics are programmed and explained in the R program "cobalt" [32].

Covariates that do not demonstrate balance, as well as covariates that will then be included in an initial multinomial logit model (with the 4 treatments as outcomes). Then using generalized propensity scores, we will develop inverse probability of treatment assignment weights. This approach will then result in estimates of average treatment effects in the response model.

2.15.3. Efficacy analysis

The primary efficacy endpoint will be the change in asthma control between Study Visit 1 and Study Visit 5 (See Online Table B1 in Online Appendix B for a description of study outcomes.). Secondary efficacy endpoints will include the change in asthma symptom days and school absences between Study Visit 1 and Study Visit 5. Although the protocol calls for regular measurement times, study outcomes will most likely have the following characteristics. (1) They will not all be administered at the planned 3,6, 9 and 12 months. For some the schedule will lag. (2) Measurements will be missed for children who skip a visit. We shall model the time of each measurement as the number of months (including factional amounts) from date of randomization. We will model time flexibly with splines, with cubic splines as needed. Knots for the spline will be assumed at time 3, 6 and 9 months, the intended dates of measurements. With time measured flexibly, and with a statistical model that includes time by treatment (4 level) interactions, the spline model will allow for estimate of differences (or ratios) of outcomes at any point along the time (x) axis by treatment group.

2.15.4. Response model—to estimate expected values over time

The response model will be a weight longitudinal model using splines for time and time by treatment interaction terms. This model will result in the estimation of expected values at any given time post randomization for any of the four treatment categories.

2.15.5. Patient-level analysis – mixed effects models

First, linear mixed effects models with random intercepts and slopes for school, and fixed effects for the school-level intervention, time, and time-by-intervention interaction (the estimate of interest) will be applied. Likewise, the main effect for the child-level intervention and a time*intervention interaction term will be included in the model, and variation across multiple measurements on a child within a school will be accounted for by child-level random effects. This approach then becomes a three-level model with explicitly modeled random effects at the school and child levels. Synergy of the effect of the two interventions will be estimated by the 3-way interaction between time, the school-level intervention, and the child-level intervention along with all corresponding two-way interactions. Models will use numerical quadrature with least 12 quadrature points. Models with 16 quadrature points will be used to check sensitivity of results to numerical integration. This and other individual-patient-level methods can be more efficient (smaller confidence bounds) than cluster (school)-level models [33]. However, mixed effects models rely on numerical integration.

We shall exploit mixed effects models to estimate the degree of variation of effects across the 36 schools, both the 18 intervention schools and the 18 control schools by estimating the random slope component of variance and asking whether the observed variation across schools is greater than that expected at random.

2.15.6. Patient-level analysis – marginal models

Second, marginal models using generalized estimating equations [34] will produce robust estimates that adjust for clustering at the school level. These methods tend to be robust for non-continuous outcomes (non-identify link models) and those outcomes will likely apply to our outcomes of asthma control (possibly a log gamma model) and number of symptom days (possible a log link Poisson or negative binomial model). Marginal models do not rely on numerical integration.

Marginal models tend to work poorly for designs with small numbers of clusters. In our case, the number of clusters (36) is relatively large. Nevertheless, we shall implement at least one method for adjusting for non-large numbers of clusters, as implemented in Stata's program xtgeebcv program [29] (Gallis 2019) and R's program "saws" [36] (Fay and Graubard 2001).

School-level analysis -- randomization-test-based methods. Third, we will implement assumption-free, randomization-test-based (permutation test) methods that do not rely on assumptions of parametric models [31–35,37].

We will use conventional levels of statistical significance ($p = 0.05$) for all pre-specified comparisons for these aims. We shall not apply Bonferroni corrections for estimates from different modeling methods that use the same specification. We shall report all results to confirm consistency of findings and their robustness to model specifications. Variability of the intervention effect across schools will reflect consistency of intervention effects and thus generalizability in new settings. Both mixed effects models and permutation-test methods [42] (Lee 2012) will estimate variance components to support generalizability. This approach will also be used to account for change over time across schools, and to assess sustainability of the proposed interventions.

All contrasts noted in specific Aims 1a through 1d are handled with the same modeling specifications. This approach will also be used to account for change over time across schools, and to assess sustainability of the proposed interventions.

2.15.7. Subgroup analysis

Mediator and Moderator Variables. Baseline variables including asthma control, BMI, school type (public/charter) and demographic characteristics which may serve as moderators of intervention effectiveness will be evaluated through subgroup analyses. These variables will be used to identify subgroups of children that may be more likely to benefit from the study interventions. Mediator variables such as communication between school and primary care and level of participation in school-based asthma therapy will be evaluated to better understand the mechanism of effect of the intervention on the study's primary outcomes. The mediation analyses explores potential mediating variables (M) on the effect of the intervention (A = navigator; S = School) on student/patient outcomes (Y) with a goal of understanding which components of the intervention, and one or more dimensions of the intervention, proves to be ineffective, then the mediation can help to identify the reasons. Mediation analysis requires many and much stronger assumptions. We shall follow the counterfactual approach [43] to mediation to take advantage of recent statistical developments in causal inference [44–50,57]. Because children are not randomized to levels of M, and to avoid the resulting potential bias, we will adopt two approaches: (1) Marginal structural models, in which mediator variables are modeled as functions of baseline covariates, have been developed for parametric estimation of direct and indirect effects without the severe assumptions of prior methods [51–54]; (2) Simulation-based methods [42] offer practical alternatives. These methods apply to clustered designs as well as traditional randomized designs [55,56]. Using the

nomenclature of recent reviews, the school intervention of our factorial design is 2-1-1, in which the intervention applies at level 2 (schools) and mediators and outcomes are measured at level 1[57]. Using these methods, we can decompose total intervention effect into the two components: natural direct effect (NDE = the effect of the intervention on child outcomes not mediated), and the natural indirect effect (NIE = the component of the intervention that seems to proceed through the measured mechanisms). As such, Total effect = NDE + NIE [52,54]. Within this framework, we can also estimate effects of multiple correlated mediators [58].

Specific Aim 4. Examine the costs, savings, and cost effectiveness associated with the intervention. These analyses will take a health care service perspective, which is of particular interest to policy makers and includes hospital, community and school-based health services. Cost-effectiveness analysis (CEA) requires the assessment of all resource use corresponding to each cost category during the study period including costs attributable to intervention implementation.

Measuring Resource Use and Costing Procedures. Relevant resources to be measured are: clinic CHW time, asthma management supplies provided to participants (bed/pillow covers, roach bait, tiles, etc.), school CHW time, and hospital, community and school-based health services utilized by children with asthma.

To measure resources related to intervention implementation, we will document intervention implementation activities of clinic and school CHWs. Intervention times will be derived from administrative records of intervention session times, and diaries completed by clinic and school CHWs during four, 1-week periods throughout the trial. Intervention activities include: For clinic CHW: asthma education, care coordination, and follow-up scheduling. For school CHW: asthma education, care coordination, and environmental assessment. The study participants will have detailed data on their utilization of intervention services over the study period as logged by the clinic and school CHWs.

Data on non-intervention health care (hospital, community and school-based health services) utilization of children with asthma will come from each of the 3 clinics participating in the study. Since children can utilize services outside of 3 participating clinics, we will collect data on all service use and other resource use from the caregivers. Caregivers will be given event diaries to record each health care visit of their child; these diaries will be collected at the end of each month. A baseline interview with caregivers covering the service use in the past six months will also be conducted.

For each component, cost of physical materials used for interventions and costs associated with time spent for intervention implementation will be calculated. Costs will be categorized as: (1) fixed fees, (2) variable fees, (3) travel/lodging, and (4) personnel. Costs will also be broken into the temporally related study periods: intervention (12 months), and sustainment (9 months). To derive costs, we will use the resource costing, which involves determining for each unit a price that reflects the real opportunity cost of the service 108.This price weight is then multiplied by the number of units at that price and then summed over all services.

The costs of CHW time will be estimated using data on average salary and benefits for those in job categories matching the staff providing these services. For materials we will use acquisition costs. Travel costs to home visits will be included. Other unit costs (i.e. outpatient visit) will be obtained as needed from published resources and national surveys. Finally, total direct costs will be calculated for each child and then averaged across children within each study arm to determine average costs per study condition.

Intervention Cost Analysis. Cost analysis aims to estimate total costs of implementing clinic and school interventions during a typical operating year; and assumes a health care service sector perspective. Average aggregate costs and range in aggregate costs across intervention arms will be examined. Cost distribution between administrative and direct services, how specific activities within a treatment modality affect costs, and variation in costs by site (school, clinic) will be explored.

Cost Offset Analysis. We predict that intervention will reduce medical costs, thereby contributing to a cost offset. We will compare cost data from pre, during and post-intervention to investigate potential cost reductions resulting from the intervention. We will estimate potential savings in medical costs resulting from changes in outcomes in each study arm. We expect most savings to occur due to reductions in emergency and inpatient hospital visits.

Cost Effectiveness Analysis. The outcomes of different study arms will be combined with their respective costs to provide a measure of relative cost-effectiveness that can be compared across study groups. The presumed effects will be improvements in child (reduction in emergency visits and hospitalizations and improvements in the asthma control measures (symptom free days)) and parent outcomes (missed work days due to child's condition). Using the estimated mean cost and mean effect per patient by intervention group, an incremental cost-effectiveness ratio (ICER) will be constructed for each outcome for which the specific intervention is shown to have a significant effect. Incremental cost-effectiveness will be computed as the ratio of the difference in mean costs (incremental cost) to the difference in mean effects (incremental effect), and will represent the additional cost per additional improvement in the outcome measure (e.g. one unit decline in ER visits), of one intervention arm compared to another. A joint distribution of incremental mean costs and effects for the intervention arms being compared will be generated using non-parametric bootstrapping 113.These data will be used to explore the probability that each treatment is optimal choice, subject to a range of possible maximum values (ceiling ratio) that a decision maker might be willing to pay for an additional improvement in child or parent outcome score. Cost-effectiveness acceptability curves (CEAC) will be generated by plotting these probabilities for a range of possible values of ceiling ratios 114,115.

2.15.8. Sample size and power

The factorial design has enhanced statistical power and can handle cluster randomization of schools. All power estimates are based on custom programmed simulations to detect power for pre-specified contrasts for each Specific Aim. Details of the simulations are presented in Online Appendix D.

2.16. Interim efficacy or safety analyses is not expected

2.16.1. Missing data

Height is not done at each encounter. For that reason, height must be carried forward from the last available measurement time. This practice, though common, can result in a bias toward higher than actual BMI over time. Adjustments (e.g., interpolation) of height for measurement times between height measures is possible. If any interpolation of height, we shall do so without regard to measures of outcome.

Missing data on other covariates will be handled using formal multiple imputation as needed. The proposed mixed effects models make limited assumptions of “missing at random” (MAR). To the extent that children are lost to follow-up, we shall include in our models covariates that are associated with the probability of dropout to limit confounding by dropout. We anticipate no school withdrawals, but in case of loss, we will use all data collected until time of dropout.

2.16.2. Proposed update to data analysis plan: impact of pandemic restrictions

The original statistical analysis plan (SAP) includes the fitting of longitudinal models to evaluate the impact of study interventions on primary and secondary outcomes in models that model time as months from randomization, with splines (knots at 0, 3, 6, 9 and 12 months)

and time by treatment interaction terms. Mixed-effects and population-averaged (GEE) models will be fitted.

The initial analyses will be conducted as planned. Sensitivity analyses will then be performed to evaluate the impact of pandemic restrictions (pre and post).

Longitudinal models for the main analyses will be modified to include an indicator variable for post COVID-19 phase with time by post Covid-19 interaction and time by post COVID-19 by intervention interaction terms. In these models, post Covid-19 phase will be included as a time varying covariate within individuals. The post COVID-19 time period is any data past March 14, 2020.

Interpretation of Longitudinal Models in Sensitivity Analyses The terms below will be evaluated in the following order:

A term will be removed from the model if not significant, only then will it be meaningful to evaluate the subsequent term(s).

Post pandemic restrictions by time by intervention interaction terms: If significant, the impact of an intervention at a particular time point (e.g. at 3 months post-randomization) depends on post pandemic status (relative to pre).

Post pandemic restrictions by time terms: If significant, the expected value of the outcome at a particular time point depends on post pandemic status (relative to pre).

Post pandemic restrictions indicator variable: If significant, the expected value of the outcome variables depends on post pandemic status (relative to pre).

3. Results

This study has completed recruitment and enrollment of participants. Enrollment is at 627 and concluded on June 30, 2021.

4. Discussion

Through this research, we aim to determine whether the evidence-based interventions are effective in this inner-city cohort for improving asthma control. While prior studies have demonstrated the value of CHWs in improving asthma control and care of children, this will be the first study to assess the potential effectiveness of CHWs in the school-based setting and potential added value of having CHWs coordinate across different settings where children receive care and spend their time. We also plan to analyze whether there are specific participant characteristics which enhance the likelihood of improvement of asthma control and whether there is a specific school climate that predisposes the school intervention to be more successful.

If proven effective, this care coordination program will assist caregivers in assessing resources, improving self-management skills, and ultimately reducing asthma-related ED visits and hospitalizations. Based on the findings of our secondary outcomes, healthcare systems, payers, and policy makers will have additional comparative data to inform decisions about how and where to focus additional resources and investments in childhood asthma care to improve outcomes for inner-city children. This design promotes a holistic approach of connecting caregivers around the patient enabling us to address clinical and social needs. Primary Care Community Health Workers are residents of the community we serve and provide not only clinical care coordination but a thorough needs assessment at baseline are able to identify unmet social needs and connect families to those resources. Through the interaction between Primary Care and School Community Health Workers we thus close the loop connecting schools, caregivers and clinicians around the patient and caregivers asthma management needs reducing fragmentation of care and ultimately improving asthma control. Limitations include the possibility of contamination among the four main intervention groups. For example, although the patients are assigned to a specific group because these patients will also encounter usual care in the practices (which includes a primary care CHW), they may also receive services that are not assigned to their group outside of the research project. We have attempted to limit this contamination by clearly identifying in the chart when the child is enrolled in this project although the clinical team will not know the randomization assignment. There is also potential contamination for caregivers of children who are assigned to receive the Primary Care CHW services, to desire to please the CHW during data collection visits. We have attempted to limit contamination by requiring a different study team member to complete data collection study visits than the assigned Primary Care CHW. We understand from the experiences of other studies that where there are highly motivated caregivers or school personnel, a group not randomized to receive an intervention may seek to implement some aspects of the asthma intervention. We will track any changes in asthma initiatives or programs in all partner schools and changes in caregiver behavior for asthma management through quantitative and qualitative methods. Another limitation of this study is that the results may not be generalizable to more rural communities. In addition, members of the West Philadelphia Asthma Care Collaborative (WEPACC) who have provided the framework and guidance for this study have been actively involved with the Community Asthma Prevention Program (CAPP) at CHOP for over a decade. Newly established community asthma programs may face greater challenges in reproducing this or a similarly designed comprehensive asthma program.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2021.100864.

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