School-Based Telemedicine Enhanced Asthma Management: A Randomized Control Trial Using Novel Technology to Improve Preventive Asthma Care

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Background:

Asthma is one of the most common chronic illnesses of childhood, affecting nearly 10% of children in the US. Asthma causes morbidity from recurrent symptoms, impairment of quality of life, limitation of activity, school absenteeism, and missed days of work for caretakers. Asthma also has a significant economic impact; direct health care costs from asthma exceeded $14 billion in 2007.

In the US, children from impoverished and minority ethnic and racial backgrounds suffer disproportionately from asthma. In fact, Black children are approximately 2.5 times more likely to have an ED visit or hospitalization for asthma than White children. The US has made a commitment to eliminate health disparities between Black and White Americans, yet numerous studies document disparities in medication use, health care utilization, and outcomes in minority patients.

It is increasingly recognized that asthma is a chronic disease characterized by inflammation in the airways, and that anti-inflammatory medications are paramount in the management of the disease and prevention of morbidity. Inhaled corticosteroids are the most effective long-term therapy for patients with persistent asthma and the NHLBI Expert Panel guidelines recommend that all patients with persistent asthma receive daily preventive anti-inflammatory medications. These medications reduce asthma symptoms, improve pulmonary function, and prevent exacerbations leading to hospitalizations when used as recommended. In addition, once medications are prescribed, the guidelines recommend follow-up assessments in 4-6 weeks, with adjustments in therapy as needed, to assure the goals of therapy are met. Specialist consultation should be considered for any child with difficulty achieving or maintaining control.

Despite clear and well-developed guidelines for care, little has been done to assure implementation of these guidelines. Many children in the US with persistent asthma symptoms do not receive preventive medications. In addition, many children who are prescribed a preventive medication do not achieve optimal control, at least in part due to poor adherence and lack of appropriate follow-up care. Consistent with other studies that have shown adherence rates to preventive medications of approximately 50%, we have found that adherence to daily medications is very low and appropriate follow-up occurs infrequently. Further, parents tend to underestimate the child's overall disease severity causing communication barriers with providers and inadequate attention to asthma care. In addition, some providers do not conform to Expert Panel recommendations and may not deliver optimal preventive care. Importantly, the greatest under-use of preventive medications and lack of appropriate asthma care occurs among poor inner-city children.

A significant amount of asthma morbidity could be prevented by sustainable improvements in the delivery of guideline based care. We have developed the School-Based Telemedicine Enhanced Asthma Management (SB-TEAM) program, which utilizes school-based directly observed therapy of preventive asthma medications, enhanced communication tools, and telemedicine to overcome key barriers to guideline-based preventive asthma care among minority, poor children residing in urban Rochester, NY. This study will allow us to build upon our prior school-based program (RSRB #12308), optimize its effectiveness, and begin to address the issue of sustainability without disruption of a highly effective collaboration.

Our prior work indicates that directly observed therapy (DOT) of preventive asthma medications can be effective at improving outcomes in pediatric asthma. Additionally, there is substantial evidence in other therapeutic settings that treatment that is directly observed can be effective. By delivering daily preventive medications through schools, adherence can be assured on the days the child attends school,

and because schools already routinely provide daily medications for other conditions such as attention deficit disorder, the provision of daily preventive asthma medications represents a conceptually simple system change to improve adherence.

Telemedicine, a system that allows clinicians to provide assessment and consultation through remote audiovisual technology, enables children to be seen by a physician without making a trip to the doctor's office or hospital. This rapidly expanding technology eliminates a significant barrier to care by making it possible for a healthcare visit to be accomplished while the child remains at school, the parent remains at work and the provider remains at their usual work place (or home). Telemedicine is used for acute illness visits as well as to monitor and address chronic conditions such as attention deficit disorder and asthma. Telemedicine is used in cities worldwide and has been used in Rochester, NY for more than 10 years, now serving all schools in the city school district with mobile telemedicine units. Additionally, there is reimbursement for telemedicine visits by local payers, making it a sustainable system of care. Telemedicine is an efficient, cost-effective, and safe way of reaching patients and facilitating access to care.

School-based programs represent a promising strategy for asthma management because of the potential to reach large numbers of children and optimize their care in the setting in which they spend most of their day. Further, collaborations with schools provide the opportunity to reach high-risk children and target those in greatest need of assistance, regardless of their contacts with the health care system. We have established a unique partnership with the city school district and its school nurses that has allowed us to develop programs for urban children with asthma over the past 10 years. Our original study (RSRB #12308), testing directly observed therapy of preventive asthma medications, included 530 children ages 3-10 years, from more than 50 elementary schools. Results from this study demonstrated reduced morbidity, decreased absenteeism, and fewer exacerbations for these very high risk children (see progress report). Our current proposal aims to expand this successful partnership through the integration of a new system of care for the sustained delivery of preventive asthma medications at school, using web-based communication technology and integrating ongoing monitoring and tailoring of the care regimen via telemedicine.

Study Objectives:

This study has the following objectives:

1. To identify and recruit an urban sample of young children, aged 3-10 years, with mild persistent to severe persistent asthma from preschool and elementary schools throughout the Rochester City School District, the Early Learning Center at Wilson Commencement Park (WCP), the Ibero Early Childhood Center, and the Volunteers of America's Children Center using web-based screening
2. To collect baseline morbidity data to characterize this group of children with asthma and determine risk factors for the frequency and severity of recurrent symptoms.
3. To randomly allocate subjects into either: 1) SB-TEAM intervention group (directly observed administration of preventive asthma medications in school and ongoing monitoring and tailoring of the care regimen using telemedicine) or 2) a control condition including enhanced usual care (eUC) (report of symptoms to PCP) with no delivery of preventive medications in school.
4. To follow subjects prospectively throughout the school year for endpoints defined by clinical outcomes (symptom severity, asthma control, health care use), functional outcomes (absenteeism, quality of life), and airway inflammation (FeNO).
5. To assess the effectiveness of the SB-TEAM intervention in reducing asthma morbidity (including symptom-free days post-intervention as the primary outcome) compared to an enhanced usual care (eUC) comparison group in school age children with persistent asthma.

6. To establish the cost-effectiveness of the intervention with a specific focus on ultimate sustainability and dissemination.

Study Overview:

This proposed project aims to improve guideline-based asthma care using enhanced communciation and screening tools, telemedicine and directly observed therapy of preventive medications in city schools. This intervention is designed to overcome key barriers to guideline-based preventive asthma care among minority, poor children in Rochester, NY. Web-based screening will be used to identify children with persistent or poorly controlled asthma and to send reports to the child's primary care doctor. Children in the SB-TEAM group will receive a telemedicine asthma assessment in school and be prescribed a daily preventive asthma medication to be taken through school-based directly observed therapy. Follow-up telemedicine visits will be completed to make dose adjustments and treatment revisions to optimize guideline based treatment. Intervention functions will be overseen by the asthma coordinator,a registered nurse with extensive training in pediatric asthma, as well as Jill S. Halterman, MD, MPH, the study's primary investigator. The overall aim of this study is to evaluate the use of the SB-TEAM intervention for improving guideline based care, enhancing adherence to effective preventive medications and at reducing morbidity among young urban children with asthma.

Study Design:

We propose a two-group randomized trial. Children in participating schools will be systematically screened for asthma severity or control using the web-based system, and 400 eligible children will be assigned randomly to either the SB-TEAM intervention (directly observed administration of preventive asthma medications in school and ongoing monitoring and tailoring of the care regimen using telemedicine) or the eUC comparison condition (asthma screening with symptom reports and guideline-based recommendations for preventive medications sent to the PCP, and systematic feedback to the PCP and caregiver to promote appropriate follow-up care). Randomization will be stratified by the use of preventive medication at baseline and a permutated block design will be used to assure an equal balance of children in each group over time. Following randomization, children will be followed prospectively and systematically for the remainder of the school year.

Subjects and Setting:

Children, 3-10 years of age, attending preschool or elementary school in the Rochester City School District, the Early Learning Center at Wilson Commencement Park, the Ibero Early Childhood Center, and the Volunteers of America's Children Center will be screened for eligibility (children at new sites will not be screened until an amendment including a letter of support from the childcare site is approved). A total of 400 children will be recruited into the study at the beginning of each school year over 4 years (2012-2016). Children from approximately 60 or more schools will participate and each child will participate over 1 school year.

Potentially eligible children will be identified in several ways. All students in pre-school and entering kindergarten have screening forms completed prior to the beginning of the school year that include parent report of asthma or breathing difficulties. In addition, all children in the RCSD have the parent's record of an asthma diagnosis included on their school "medical-alert" forms. School nurses and health aides will identify children that present to their office with asthma or breathing problems. Similarly, the nurses or health advocates at Wilson Commencement Park, Ibero and the Volunteer's of America will identify children who present to her office with asthma or breathing problems. In partnership with the RCSD, the screening forms, medical-alert forms, and nurses' reports will be available to the study team between the end of the summer and beginning of the school year. A memorandum of agreement with

our study team has been in place for many years, and all school district rules and regulations regarding student confidentiality will be followed. Nurses, health aides, and study team personnel may also speak with parents about the program during health fairs, parent orientation sessions, or other similar events. We will also hang flyers at participating sites to allow interested parents to contact the study team directly. Lastly, the study team may contact families that have agreed to be approached about future studies (RSRB# 31010). Children who are identified as having asthma or breathing problems will be screened for eligibility by the school nurses, the health advocates or study team (see details below regarding Flagging and Screening Procedures).

Inclusion Criteria (all 4 criteria must be met):

1. Physician-diagnosed asthma (based on parent report).
2. Persistent asthma or poor asthma control (based on NHLBI guidelines[10]). Any 1 of the following:
    a. In past month, >2 days per week with asthma symptoms
    b. >2 days per week with rescue medication use
    c. >2 days per month with nighttime awakenings (for children who are not taking a controller asthma medication) OR ≥2 days per month with nighttime awakenings (for children who are currently taking a controller asthma medication)
    d. ≥2 asthma episodes during the past year that required systemic corticosteroids.
3. Age ≥3 and ≤10 years.
4. Attending school in Rochester City School District preschools or elementary schools.

Exclusion Criteria:

1. Inability to speak and understand English or Spanish (Spanish subjects will not be enrolled until an amendment providing translated documents is approved). (*Parents unable to read will be eligible, and all instruments will be given verbally.)
2. No access to a phone for follow-up surveys (either at the subject's home or an easily accessible location).
3. Family planning to leave the district within fewer than 6 months.
4. The child having other significant medical conditions, including congenital heart disease, cystic fibrosis, or other chronic lung disease, that could interfere with the assessment of asthma-related measures.
5. Children in foster care or other situations in which consent cannot be obtained from a guardian.
6. Child or sibling living in the same home was previously enrolled in this study.

Based on our prior studies, we anticipate <10% of subjects to be excluded based on these criteria.

The recruitment goal for this study is to enroll 400 children using the Inclusion/Exclusion criteria stated above. For the purposes of the University of Rochester's Research Subject's Review Board, we will also consider each child's caregiver as a subjects of this study (400 subjects), as well as school health staff members who complete evaluations at the end of this study (approximately 50 subjects), and participating healthcare providers who will be surveyed at the end of the study (approximately 50 subjects). Therefore, we anticipate approximately 900 "subjects" will be included in this study.

Study Procedures:

1. Flagging and Screening Procedures

Flagging and screening of potential participants will occur in several ways with the assistance of the school nurses, health aides and administrators (all referred to as "school nurses" below), the asthma coordinator, and the study team. To test this intervention as intended in a real-world setting, we anticipate that most of the flagging and screening will be conducted by the school nurse or asthma coordinator. The school nurses or asthma coordinator will systematically identify and screen children with persistent asthma through a previously-tested web application. The school nurse, asthma coordinator, or study team (as needed) will also conduct a more thorough screening survey to assess eligibility criteria for this study prior to enrollment. If children are found to have mild symptoms (and therefore are not eligible for the study), the children may be re-screened by the school nurse or asthma coordinator to re-assess asthma symptoms at a later time during the screening and enrollment period. Screening and enrollment will occur each year in a rolling fashion from late August through November to enroll all children prior to the onset of peak winter season.

Prior to flagging/screening, the RSCD screening forms and medical-alert forms will be used to populate a student registry into the secure web application. The school nurses may also add children into the registry based on the nurse's knowledge of students' health status at his/her school (i.e. if the child has frequent visits to the nurse's office for asthma attacks). The school nurses may only view and edit information in the web application for children at their school.

Screening process #1: The school nurse will log in the secure web screening application and complete a brief flagging survey based on the child's school health forms, conversations with parents, and other indicators of asthma (asthma related visits to the nurse, rescue medication use in school, etc.). The school nurse will record this information into a form of the web application to identify potentially eligible children. When possible, the school nurse will also speak with the caregivers of the potentially eligible children to conduct a thorough screening survey to assess the child's asthma severity or control. If the child has persistent asthma symptoms, and therefore is eligible to participate in the study, the school nurse will ask permission for the study team to call to introduce the study and schedule a home visit. The flagging and screening information will be available to the asthma coordinator and the study team via the web-based system (used in our prior SB-PACT study RSBR #32479).

Screening process #2: If school nurses are unable to complete the brief flagging form, the asthma coordinator or study team member will review the RSCD screening forms, medical-alert forms, and nurse's reports to identify potentially eligible children. The asthma coordinator or the study team member will contact the child's caregiver to assess whether the child meets the eligibility criteria, introduce the study, and schedule a home visit.

If the web application is down at the time of a screening, paper versions of the screening/eligibility form will be used and the data will later be transcribed into the web application.

2. Baseline Assessment

Research assistants will describe the study over the telephone, and subsequently conduct home visits to describe the program in detail, obtain caregiver written consent, assent from children ≥7 years, and conduct a baseline assessment. The baseline evaluation will include: an assessment of asthma symptoms, secondhand smoke exposure, home environment/triggers, standard family and health history variables, and additional pertinent covariates. The baseline survey will be read aloud to caregivers. We will obtain a saliva sample from each child to objectively measure environmental tobacco smoke exposure through the biomarker cotinine, and we will also obtain exhaled nitric oxide (eNO) measurements from each child in order to objectively measure airway inflammation. An asthma

symptom diary will be given to the caregiver for tracking of asthma symptoms throughout the school year. All families will also receive handouts for asthma resources, mental health resources in the community and smoking cessation resources. For home interviews in which the child is not present, we will obtain the parent's permission to meet with the child at the school nurse's office to obtain assent (if necessary), and collect the cotinine and eNO measures. For children randomized to the treatment condition (see below), the baseline assessment will include a detailed asthma medication reconciliation and verification of the child's insurance information.

In instances where a caregiver states that their child (age ≥7 years) is unable to provide assent to the study (e.g., a child with autism), the assent form will be waived and the research assistant will document the reason for the assent waiver in the subject's study chart.

In instances when the caregiver who provided consent is unavailable for follow-up, if a different caregiver would prefer to respond to the follow-up assessments, the study will be described in detail and verbal consent will be obtained over the telephone from the new caregiver for completion of the follow-up survey. In rare instances where the child's caregiver changes, written consent will be obtained from the new caregiver.

Participants will be given the option to allow for future contact for other research studies at the time of consent. All participants who provided permission will be added to a future contact database dedicated to childhood asthma research (RSRB #31010).

3. Randomization

Following completion of the baseline assessment, each child will be randomly assigned to either the SB-TEAM group or the enhanced usual care (eUC) group. Randomization will be stratified by the use of a preventive asthma medication, per parent report, at baseline. 200 children in both the SB-TEAM group and the usual care group will be randomized. A permutated block design will be used to assure an equal balance of children in each group over time. The randomization scheme will be independently developed by the Biostatistics Center, and the interviewer will call the Study Coordinator who will provide the subject's ID number and treatment assignment.

A) <u>SB-TEAM Group:</u>

Once randomized, the study coordinator will use the web-based system or fax to send a symptom report from the screening assessment and notification of enrollment in the study to the child's primary care provider (PCP). This report will include an explanation of the processes of the SB-TEAM program and will advise them to continue to care for the child's healthcare needs as usual. In collaboration with the telemedicine program, the study team will schedule children in the SB-TEAM group for a telemedicine visit in the school health office at the start of the school year (within 2 weeks of the baseline visit) to provide an initial assessment and determine the starting medication to be used for directly observed therapy. Telemedicine is established in the Rochester City Schools, and is currently used for acute care (i.e. illness visits for ear pain, sore throat, rashes) as well as chronic care (ADHD, asthma). We will incorporate the process for this study into the standard telemedicine system, to assure appropriate medical assessment and follow-up for guideline based asthma care delivery. Appointments for all visits are scheduled in conjunction with the child's caregiver, who may join the child at school for the visit if desired. The school site portion of the visit will be completed by certified telemedicine assistants (CTAs) who already work in the district. As per the 'usual' telemedicine protocol in the schools, the CTA will bring the mobile telemedicine unit and meet with the child at school, will enter information regarding the child's symptoms and

triggers (collected at screening) into the system, and will upload the physical examination including medical images, height/weight, breath sounds, and spirometry measurements (if a spirometer is available and the child is able to perform this test). This visit information will be securely stored in the telemedicine system's "virtual waiting room" until a provider is ready to complete the visit (visits do not need to be completed in 'real time'). Using the scheduling system pre-established by the telemedicine program and coordinated with the medical practices that provide telemedicine visits, a provider will be notified that a child's visit is available in the "virtual waiting room". The provider will log on to the telemedicine system from their office and perform the visit by reviewing the symptom information collected, viewing the child's images, and listening to the breath sounds. The telemedicine provider will then contact the child's caregiver via telephone to further discuss the child's asthma and develop a treatment plan. The telemedicine provider will deliver brief asthma education (eg; trigger avoidance, symptom monitoring) and referrals to community resources as needed, and will send a guideline-based preventive medication prescription electronically to a local pharmacy through the telemedicine system. After the visit, a summary of the assessment and treatment plan will be sent to the parent (through the school) and faxed through the system to the child's PCP for inclusion in the medical record. The telemedicine assessment at school will approximate care that would be delivered at an outpatient asthma visit and will use a standard asthma visit template; visits take approx. 20 minutes. Reimbursement will be submitted to the child's health insurance, similar to a standard asthma visit (Rochester payers reimburse for telemedicine visits).

Several clinicians routinely perform telemedicine visits as part of our current system, through 4 different practices that serve >60% of the children living in the city of Rochester. We will schedule asthma visits with the child's primary care practice when possible. If there is no telemedicine provider at the child's practice (or if the provider is unavailable for the visit), several providers are routinely available to perform visits; this scheduling system is well received and works very efficiently.

All of the children in the study must have persistent asthma symptoms upon enrollment, and thus warrant the use of a daily preventive asthma medication. The starting medication will vary depending on the child's baseline asthma therapy and will be determined by the treating provider. Prescriptions will be sent to pharmacies that provide delivery services with an automated message indicating one canister of preventive medication, with a spacer and mask as appropriate, to be delivered to the family for medication doses on weekends and days the child does not attend school, and a second canister to be delivered to the child's school nurse or health aide for administration of one dose at school on the days in which the child attends school. Most children will receive once daily dosing since it is effective and will allow for administration of medication during school hours; if more frequent dosing is needed the additional dose will be given at home. The time of dose delivery will vary based on the school, and will coincide with the most convenient time for the student and nurse. While many schools do not have a full time nurse, all schools are prepared for medication administration as many children have daily medication needs (e.g. medications for attention deficit disorder). In our prior study, medications were administered >95% of the time the child was in school. All children will be instructed to rinse their mouth with water after each medication dose. A medication dispensing log will be used for tracking purposes. While adherence will be assured by the nurse on the days the child attends school, adherence will simply be encouraged on days the child does not attend school.

Medications:

Initial Medication – All of the children in the study must have persistent asthma symptoms upon enrollment, and thus warrant the use of a daily preventive asthma medication according to the NHLBI guidelines. All medications will be prescribed by the child's telemedicine provider after a complete asthma assessment. While standard doses of medications will be recommended (see examples below) the starting medication administered through the study will vary depending on the child's baseline asthma therapy and will be prescribed at the discretion of the telemedicine provider in agreement with the child's caregiver.

Although children may use any FDA approved daily preventive asthma medication as part of this study, we anticipate that most children will be using Flovent®, Advair® or Pulmicort® as these are the most common asthma medications used in Rochester.

Examples of medications and doses that likely will be prescribed for this study:

Flovent® 110 mcg, 2 puffs, once a day
Advair® 250/50 mcg diskus (DPI), 1 inhalation, once a day
Advair® 115/21mcg inhaler, 2 puffs, once a day
Pulmicort® 180 mcg Flexhaler (DPI), 2 inhalations, once a day

After each telemedicine visit, the asthma coordinator will carefully review each child's asthma medication and dose, and will assure that appropriate preventive medications has been prescribed according to NHLBI guidelines.

Follow-Up Telemedicine Asthma Control Assessments and Medication Adjustments– Follow-up telemedicine assessments will occur twice during the study period. Follow-up visits will be scheduled at school 4-6 weeks after initiating DOT, and again 4-6 weeks later. These visits will focus on assessment of control, assessment of ongoing triggers or co-morbid conditions that might interfere with an optimal response to treatment, and brief asthma education. The telemedicine provider will also assess for any medication-related side effects (oral thrush, growth monitoring). Guideline-based medication adjustments (or specialist referral, if appropriate) will be recommended for children who continue to have persistent symptoms despite DOT in school. Information regarding changes in the child's regimen will be discussed with caregivers and reports will be sent to the PCP.

We do not anticipate the opportunity to step-down therapy, since all children will have persistent symptoms at the start of the trial and could benefit from several months of anti-inflammatory therapy. A natural time for discontinuing or stepping-down therapy occurs at the end of the school year when the children will no longer be receiving medications through school. Two weeks prior to the close of the study, we will notify both PCPs and families that children receiving preventive medications at school no longer will receive medications through the study. PCPs will be directed to provide ongoing medication management as needed.

The medications and spacers (if needed) will be purchased through the child's health insurance. Based on our prior research, we anticipate that most of the children will have some form of either private or public health insurance, with most being insured by Medicaid. If a family does not have insurance or insurance coverage status is uncertain, if there is an unexpected expense despite insurance coverage, and when a family informs us they are unable to pay for the co-payment, we will pay for medications or medication supplies (e.g., spacer, nebulizer mask, etc.). In all instances we will also assist the family in getting insurance, help them to proactively plan for refills of medications, as well as link them with services to help them afford co-payments.

Referrals to Additional Resources:
In the SB-TEAM, the telemedicine provider may also provide referrals to an asthma specialist, Regional Community Asthma Network (RCAN), and New York State Smokers' Quitline, as appropriate.

B) Enhanced Usual Care (eUC) Group:
Similar to children in the SB-TEAM group, children in the enhanced usual care group will receive a symptom assessment using national care guidelines, a recommendation for appropriate preventive medications, and asthma education materials. After screening, baseline and randomization, we will use the web-based screening and report system or fax to send a symptom report to the child's PCP with guideline-based recommendations for preventive care. We also will give all providers a summary of the most current national guidelines. We will provide systematic feedback to the family and providers at the same intervals as in the SB-TEAM group's telemedicine visits, by prompting providers to use care guidelines, and caregivers to schedule recommended follow-up visits with the PCP. PCPs of children in the eUC group will assume responsibility for prescribing appropriate medications during the study. In our prior studies, children in the eUC group improved over time, thus creating a conservative bias.

4. Follow-Up Assessments
We will follow subjects prospectively through the end of the school year, which will vary from between 7-9 months depending on the timing of enrollment for each subject. The preliminary effectiveness of the study will be assessed by telephone interviews with the caregivers, medical record review, and review of school records including, absenteeism, school nurse records (e.g., visits to nurse, medication use at school), and academic performance records. Research assistants, blinded to the subject's group allocation, will conduct telephone calls with caregivers every other month following the initial baseline to collect the follow-up data. At the end of the study year, a home visit will be conducted for the final follow-up assessment at the end of the school year. While the intervention will only last 7-9 months, we may follow subjects for up to 5 years post their enrollment into the study to collect additional outcome measures. These measures may include medical chart review or additional survey assessments with the primary caregiver. If additional surveys are conducted with the caregiver, we will request verbal permission from the caregiver prior to collecting survey data.

Evaluations will be conducted with school health staff members who administered directly observed therapy to children enrolled in the program and/or completed assessments using the web-based system. Paper surveys will be distributed prior to the end of each school year. Respondents will be asked to complete the survey within a 2 week window and return via fax.

Healthcare providers whose patient(s) were enrolled in the program will also be asked to complete a short evaluation asking for feedback on the process. These surveys will be administered on paper and returned via fax and as a web-based survey with an email invitation.

We will also complete semi-structured interviews with participating school health staff and healthcare providers to gather additional information on program acceptability.

5. Measures
The table below summarizes the outcome measures and covariates that will be collected for this study. The table includes how the data will be collected, validated scales/instruments used, and times of administration.

Clinical Outcomes	Measurement Strategy	Time of Administration
Symptom Severity	Caregiver interview, NHLBI guideline-based items Asthma Control Test (ACT)	Baseline, each follow-up, final Baseline, follow-up 2, final
Health Care Utilization	Caregiver interview – health care utilization survey Review of medical chart and pharmacy records	Baseline, each follow-up Conclusion of Study
Airway Inflammation	Objective measurement: FeNO	Baseline, follow-up 2, final
Pulmonary Function	Spirometry	Baseline, follow-up 2, final
Functional Outcomes		
School Absenteeism	Caregiver interview School record review	Baseline, each follow-up Conclusion of study
Quality of Life	Caregiver interview-*PACQLQ*	Baseline, each follow-up
Potential Mediators		
Adherence	Caregiver interview-*Horne Adherence Scale* *Pharmacy Data*	Baseline, each follow-up End of study
Communication with Providers	Caregiver interview-PEPPI	Baseline, final
Satisfaction with Medical Care	Caregiver interview-PSQ-18	Baseline, final
Independent Variables		
Demographic, Medical Variables	Caregiver interview	Baseline
Caregiver Depression*	Caregiver interview-*CES-D*	Baseline, final survey
Environmental Allergens	Environmental survey	Baseline
Secondhand Smoke	Caregiver interview Salivary Cotinine measurement	Baseline, each follow-up Baseline, final
Process Evaluation		
Training of School Nurses, CTAs, and Providers	Time to train nurses to deliver DOT with proper inhaler technique, train CTAs for asthma assessments, and providers for reinforcement of guideline based asthma care	Tracking logs for entire study period
Medication Delivery to School	Tracking log of days required to deliver medications to school and home and initiate DOT; both at beginning of the study and for follow-up adjustments	Treatment group only – tracking log
Percent of Days Children Receive Medications via DOT	Nurse medication administration logs	Treatment group only – collected at the end of the school year
<u>Diffusion of Innovations Summary Measures</u> Relative Advantage, Compatibility, Simplicity, Trialability, Observable Results	Semi-structured interview: parents, nurses, administrators, PCPs Perceived Attributes scale[12] (for school nurses, health aides, and administrators)	At conclusion of study

**All Families will be provided a list of local mental health resources at the beginning of this study.*

<u>Fraction of Exhaled Nitric Oxide (FeNO):</u>

Fraction of Exhaled Nitric Oxide (FeNO) measurement is a non-invasive measure of lung inflammation. This inflammation could be caused by many factors including colds, pollutant exposures, and asthma. FeNO will be measured using the NIOX MINO® Airway Inflammation Monitor, an electrochemical hand-

held device that instantly analyzes exhaled air for NO concentration. Children will be asked to first fully exhale and then to take a fast and deep inhalation through a disposable mouthpiece attached to the device. Then, we will ask children to exhale slowly and steadily through the mouthpiece. If done correctly, a reading will appear on the screen which will be recorded manually. FeNO will be measured 3 times, once at the baseline visit, at 4-month follow-up, and then again at the end of the school year. Some children may have difficulty with this procedure; we will only include data for children who are able to perform the procedure accurately.

Secondary Smoke Exposure: Saliva Sample Collection for Measurement of Cotinine:
Exposure to secondhand smoke will be assessed by both interview survey and cotinine measurements. At the beginning and the end of the program, a member of the research team will collect salivary fluid samples from each child using the Sorbette fluid specimen collection device, which consists of a small sterile swab mounted on the end of a 5.5 cm plastic handle. Collection will be made according to a standard protocol developed for use with children. Salivary samples will be stored frozen and shipped via courier to Salimetrics, LLC in State College, PA for analysis. The cotinine results will be recorded as an outcome measure, and will be available to families only by request. However, all families will receive resources on how to stop smoking and prevent smoke exposure.

6. Compensation
Each participating parent will be paid $20 after completion of the baseline assessment. Subjects will also be mailed $20 after each of the telephone follow-up surveys and $50 after the final follow-up survey. Total payment will be no more than $130. Payment to participants will be in the form of a Wegman's grocery store gift certificate.

Healthcare providers who complete an evaluation at the end of the program will be mailed a $5 Starbucks gift card to thank them for their time.

There may be some cost to participate in this study. Participants in the SB-TEAM group will be responsible to purchase each medication and spacer that is dispensed as part of this study as well as any fees associated with telemedicine visits (e.g., co-pays etc.) completed through the study (these are medical processes that should occur according to the national guidelines regardless of the child's participation in the study). Based on our prior work with this population, we anticipate that most of the children will have some form of health insurance to cover the cost of visits and the medications with minimal or no co-pay fee. In our prior studies we found that approximately 70% of families in the RCSD were insured with Medicaid which often eliminates co-pay fees for medications and care. If a child (in either group) does not have insurance, the study team will help the family secure health insurance. If a child in the SB-TEAM group is unable to obtain health insurance, the study team will pay for the participant's medication and spacer for the program. If there is no insurance reimbursement for the telemedicine visit, subjects will not be asked to pay any additional costs. Participants and their insurance company will be responsible for the cost of all standard of care office visits and additional medications prescribed by their PCP.

7. Data Storage and Confidentiality
To maintain the integrity, security, and confidentially of study data, the data will be maintained in a secure and encrypted web-based database and/or a password protected database on a secure university network drive. No subject data will be stored on the internal hard drives of any Strong Health computers. After data validation and analysis, subject information will be de-identified. All consent

forms, paper surveys and additional correspondence will be stored in a locked filing cabinet in a locked hallway or locked office, and will only be accessible by the study staff.

Baseline, follow-up, and chart review data will be entered into a password-protected Microsoft Access database. This database is stored on a secure university network drive that is only accessible by the research team whom must use their NetID and password to access the database. Data may also be collected using RedCap, a secure, password protected database (using University NetID's and passwords) hosted through the University of Rochester.

The screening data and PCP reports will be entered and/or generated through a secure password-protected website created and managed by SophiTEC, a consulting and web design company that manages several web applications for the Rochester City School District and other clinical research projects. RCSD school nurses and the nurses or health advocates at Wilson Commencement Park, Ibero and the Volunteer's of America will have limited access to the web-based system to edit or review information for only the children/participants in their care. Study personnel and school nurses will each have their own unique login to the system. SophiTEC will manage and maintain study data backups. The web application will utilize high grade encryption, and prior to any internet transmission, the webpage will be encrypted. Timeout systems will also be in place to expire viewing data on the webpage.

Portions of the final assessments with caregivers, nurses, and healthcare providers may be tape recorded. These recordings will be saved on a university network drive that is only accessible by study personnel whom must use their NetID and password to access these tape recordings. Once the recordings have been transcribed, they will be deleted from the network drive.

The Rochester City School District has partnered with the University of Rochester study team for this study, and all of the procedures follow the school district's rules of privacy and confidentiality, as outlined in the letter from Dr. Jeanette Silvers, Chief of Accountability for the Rochester City School District. As deputies of the school district, the study team is granted permission to review limited student information and contact families to inquire about their willingness to participate in the study.

8. Safety

This is ***not*** a drug investigational study since the effectiveness and safety of the FDA approved drugs that will be authorized/prescribed are already established and are not being tested. The intervention proposed should pose minimal risk to the children, since the medications that will be delivered at school for the children in the intervention group are medications that are recommended as the standard of care for children with the degree of asthma symptom severity required for enrollment into the program and are prescribed at the discretion of a pediatric health care provider. The most common side effects of inhaled corticosteroids, including yeast infection of the mouth and facial rash, will be assessed during each follow-up interview and during the telemedicine assessments. All children will be instructed to rinse their mouth with water after each dose of medication to prevent these side effects. Any significant concerns will be relayed promptly to the study coordinator, the principal investigator, the child's primary care provider, the study DSMB, and the Research Subject's Review Board. There is a potential but small risk of adverse effects on linear growth from the use of inhaled steroids; however, this risk is felt to be outweighed by the benefits for children with persistent asthma. In general, these medications are well tolerated and safe, and most studies do *not* demonstrate a negative effect on growth with moderate dosages of inhaled corticosteroids, that will be used in this study. The frequency and severity of all reported adverse events will be systematically recorded. Assessment of potential adverse effects will be completed at each telemedicine visit and telephone interviewers will inquire about any adverse

events, and specifically ask about any yeast infections of the mouth and facial rash. Any child (in either group) experiencing an acute asthma exacerbation at the time of a home visit or follow-up phone call will be referred immediately to their primary care provider for care. In addition, school nurses will be instructed to contact the parent of any child presenting to the nurses office with acute symptoms and refer them promptly to their primary care provider.

At home visits, research assistants will make efforts to protect subject privacy and confidentiality. The research assistants will assure that the subject is comfortable answering questions and discussing the study prior to completion of consent or any study measures If it is suspected that someone in the home may cause serious harm to themselves or others, the study team will report these issues to the study coordinator and the principal investigator who may be mandated to report these concerns to appropriate authorities. There is also a risk that the study team may discover an unknown medical condition. If this is to occur, we will refer the family to their PCP or another appropriate health care professional for evaluation and treatment.

The study team will receive safety training yearly from key study personnel and safety plans for home visits will be created (including traveling in pairs, safe words for emergency situations, and procedures for notifying and updating coordinators about whereabouts). Additionally, these procedures are outlined in a team training manual given to all employees. The study team will also receive cultural awareness training from key study personnel prior to completing home visits.

Data Safety Monitoring Plan (DSMP):
This study also includes a Data Safety Monitoring Plan as submitted to and approved by the study sponsor: National Institutes of Health and National Heart, Lung, and Blood Institute. A formal Data Safety and Monitoring Board has been assembled for this project. The plan for safety and monitoring is as follows.

9. Data and Safety Monitoring

Data Quality Monitoring

The research associates will be responsible for all data collected during the home assessments. They will receive training from key study personnel regarding asthma terminology, symptoms, medication understanding, and environmental assessment. They also will be trained by the senior project coordinator on the use of equipment for cotinine measurements and the NIOX MINO® instrument for collection of exhaled nitric oxide.

The senior project coordinator and project coordinators are all experienced in asthma terminology, symptoms and other aspects of the illness and have extensive training in research methods. They will oversee the data collection methods and all data will be reviewed by the study coordinators. Data forms will be completed at each study home visit or telephone interview and will be returned with a cover sheet and other source documentation support materials (informed consent, contact information, etc.). Pre-intervention training of study staff will be conducted to increase knowledge about asthma, asthma medications, and other important information in order to reduce the number of “real-time” data collection errors. Through this training, staff will note any inconsistencies in parent reported data and will discuss them with the parent at the time of the interview.

Key study personnel will perform all follow-up interviews and follow-up data management. These data will be collected by the follow-up research associates who are independent from the research associate recruiters, and thus we will be able to perform blinded assessments of outcomes. Our team, including the principal investigator, senior project coordinator, and recruitment and follow-up project

coordinators, have a prior record of high-quality data collection and management. We tracked over 500 children in our prior school-based randomized trial, and completed follow-ups with 93% of subjects. Treatment group assignment will not be included with any follow-up materials in order to ensure blinding of the outcome assessment.

Once forms have been collected, errors that can be corrected over the telephone (legibility, incorrect dates, etc.) will be done using telephone interviews. Forms will be keypunched into the database using a double-entry system technique and checklists will be used to ensure that all data forms have been received and entered into the database. Simple range checks as well as cross-form validation checks will be performed to ensure the accuracy and completeness of the data. A list of all data checks performed will be maintained and any errors detected by this method will be noted on the form in red ink (initials and date of change). In addition, data forms, valid informed consent documents for each enrolled patient, and supporting source documentation materials will be reviewed by the research associates for accuracy. Required regulatory documents (IRB approval, updates to the protocol, data monitoring documents) will be maintained by the senior study coordinator. All events during the course of the trial including study enrollments, adverse events and study terminations will be reported to the senior study coordinator.

Safety Monitoring Plan

A Data Safety Monitoring Board (DSMB) including a pulmonologist (Sande Okelo, MD; Division of Pediatric Pulmonology, University of California Los Angeles), a general pediatrician and health services researcher (Ruchi Gupta, MD, MPH; Division of General Pediatrics, Children's Memorial Hospital at Northwestern University), and a human subjects specialist (Nicholas Ferraio, MS, MPA; Department of Pediatrics, University of Rochester), has been assembled to provide ongoing oversight of the study. The DSMB will meet bi-annually or more frequently as needed to review study procedures and data. Potential risks related to participation in this study are minimal since the medications delivered through this program are routinely recommended by national guidelines for asthma care. In our previous school-based asthma program, which included 530 children, there were no reports of significant adverse events. The frequency and severity of all reported adverse events will be systematically recorded at each follow-up interview. Telephone interviewers will inquire about any adverse events, and specifically ask about any yeast infections of the mouth and facial rash. Any significant adverse events will be flagged by the follow-up research associates and relayed promptly to the senior study coordinator, the principal investigator, the child's primary care provider, the Institutional Review Board, the DSMB, and the NIH within 24 hours. We will hold bi-weekly research review meetings with the study team to provide an additional layer of monitoring to ensure subject safety as well as treatment integrity.

If a caregiver reports significant depressive symptoms or unusual circumstances (i.e., difficulty providing food or shelter for the family), we will offer the caregiver mental health or community resources and encourage the caregiver to contact their physician, a resource, or other trusted party. We will also offer to have a research nurse call the caregiver and provide additional support, if needed. The research nurse, trained in mental health counseling, will also determine if there are any immediate needs of the family and will advise the family and research team on next steps.

All records will be kept strictly confidential as required by the policies and procedures of the University of Rochester where data are collected, processed, or reported.

10. Potential Benefits

Potential benefits for participants of the randomized trial exist for both groups of children (SB-TEAM and eUC). The goal is for children in the SB-TEAM group to have improved symptom assessment, adherence

to preventive medications, and appropriate tailoring of therapy, thus they may experience less morbidity from asthma. Although children in the eUC group will not be receiving medication through school or telemedicine asthma visits, we will prompt their PCP to provide guideline based asthma care including prescription of the appropriate preventive medications and will provide regular reminders to PCPs and caregivers to care for the child's asthma. Improved asthma management should result in reduced morbidity for these children. Since the medications used in this study are safe and effective at the doses administered, and are strongly recommended by the national asthma guidelines, we anticipate that the intervention benefits will outweigh the minimal risk of participation.

11. Analysis

Sample Size:

This study is designed to have adequate power to detect the smallest clinically significant difference in mean SFDs post-intervention between the intervention and enhanced usual care groups. Based on our previous data, we estimate the pooled standard deviation of SFD at 2.8 and within-subject correlation at 0.3. Power was calculated for the intervention effect on SFD with at least two assessments for each subject. We anticipate <15% attrition, as attrition was minimal (<10%) in the prior study, and therefore plan to enroll 400 children. With a final sample of 336, we will have 90% power to detect a difference of 0.8 symptom-free days or greater per 2-wk. period. This difference is supported by our prior data, and would justify continuing the intervention. There are more than 11,000 students in pre-k through 4th grade in the RCSD and at least 6,600 entering kindergarteners in a 3 year period. Conservatively assuming an asthma prevalence of 9%, more than 1,584 students have asthma, and approximately ½ of these students (792) have persistent asthma. In our prior study, we enrolled 74% of eligible subjects. A conservative estimate would allow us to enroll 120 subjects/year (60%), which is more than adequate to meet our sample size.

Primary Analysis:

The primary analysis of this study aims to assess the effectiveness of the SB-TEAM intervention in reducing asthma morbidity (including symptom-free days post-intervention (follow-ups at 4 mo, 6mo and final)as the primary outcome) compared to an enhanced usual care comparison group in school age children with persistent asthma. We will follow subjects prospectively throughout the school year for clinical outcomes (symptoms, asthma control, health care use), functional outcomes (absenteeism, quality of life), and airway inflammation (FeNO). We will use graphical and numerical summaries to describe the outcomes at each assessment point. If distributional assumptions associated with a particular statistical procedure are violated, appropriate transformations will be made or non-parametric alternatives will be used. In accordance with the intention-to-treat principle, all randomized subjects will be analyzed within the group to which they were assigned; minimal crossover is expected. Hypothesis-driven comparisons will be made to control the family-wise type I error rate at 0.05 (two-sided) for the primary hypothesis.

We will determine whether there are important differences at baseline despite randomization between the SB-TEAM and eUC groups in demographics and background characteristics (age, race, ethnicity, insurance, caretaker education), depression, and cotinine. This will include t-tests (or Wilcoxon Rank Sum test) for continuous variables and chi-square (or Fisher's Exact) tests for discrete variables. These comparisons will enable the identification of control variables for use in analyses evaluating treatment effect.

To test for differences between the SB-TEAM and eUC groups on clinical and functional outcomes at the primary time point, bivariate comparisons will be made using t-tests for continuous variables (number of symptom-free days (SFD), symptom nights, rescue medication use, days absent, quality of life, FeNO,

and ACT scores), and chi-square tests for discrete variables (acute visits, hospitalizations). In addition, the time-course of treatment response during the follow-up period will be evaluated using a linear mixed model with the primary outcome, SFD at post-intervention, as the response, and treatment condition, treatment by time interaction as independent variables. We will model the repeated assessment post-intervention and assess post treatment effects as well as maintenance gain during the period using appropriate linear contrasts. The analysis will be controlled for baseline symptoms, and variables that are found to differentiate between groups at baseline. The treatment effect will be regarded as fixed and the subjects will be modeled as random effect, with an appropriate variance covariance structure specified. Secondary continuous outcomes will be analyzed in a similar manner. Discrete outcomes will be analyzed by fitting Generalized Estimating Equation model. Appropriate link functions and response probability distributions will be specified.

We will also consider whether certain process measures from our conceptual framework (adherence, patient/provider communication, satisfaction with medical care) act as mediators in the relationship between the intervention and outcomes. Thus we will estimate both the direct intervention effect on the outcomes, as well as the indirect effect through process mediators. For each purported mediator, we will use structural equation models (SEM) to model its relationship to treatment and primary outcome. SEM can quantify both direct relationships between latent traits, the effects of factors that modify these relationships, and also indirect relationships mediated by other factors. Potential confounders such as baseline symptoms will be included as covariates. Maximum Likelihood (ML) will be used for estimation. Goodness-of-fit will be assessed in a two-level process. In the first level, the fit of the unrestricted model will be tested using standard diagnostic measures for linear regression. In level two, the appropriateness of assumption of the proposed structural equation model will be investigated by testing this model against the unrestricted model. The following indicators will be used: (a) Comparative Fit Index (CFI), (b) Non-Normed Fit Index and (c) Root Mean Square Error of Approximation. We will use chi-square statistics for the structural invariance tests to determine effect modifiers. These analyses will aid in our understanding of pathways by which SB-TEAM impacts outcomes.

The primary analyses will be performed according to the intention-to-treat principle and will include all randomized subjects. Substantial attention will be invested in participant retention; reasons for any subject withdrawals that may occur will be carefully documented. Missing data patterns will be examined by comparing subjects who discontinued with those who remained in the study. Inference based on the proposed methods GEE and/or LMM is valid provided that missing data follows the missing completely at random (MCAR) assumption. However, if the occurrence of missing data depends on the observed response but is independent of unobserved data (MAR), weight GEE (WGEE) will be used. Sensitivity analysis to MAR assumption will also be carried out.

Cost Effectiveness Analysis: *Establish the cost-effectiveness of the intervention with a specific focus on ultimate sustainability and dissemination.* We will assess health and economic benefits of SB-TEAM from both the societal and the Medicaid perspective. We also will use *Diffusion of Innovations Theory* to help understand how this innovative model can be maintained in the current system of care through city schools.

We will assess health and economic benefits of SB-TEAM compared to enhanced usual care by using cost-effectiveness (CE) methodology. The time horizon of the study will be one school year (September-June). Four cohorts that will complete the study in consecutive years will be analyzed as one stacked study cohort. The basecase analysis will be conducted from the societal perspective which includes all identifiable costs and benefits, regardless of whom they impact. The majority of children in the study

are eligible for Medicaid (73% based on the prior study), thus a second analysis will take the Medicaid perspective. The benefits of the intervention will be measured as the number of symptom-free days during the school year.

Three main categories of costs to be considered include programmatic costs, productivity costs, and medical costs estimated at the individual child level. Programmatic costs include costs of initiating and running the program, hiring and training staff, purchasing or leasing equipment, staff travel, and information system costs. Costs associated with this study that would not exist as part of the intervention will not be included, as we do not anticipate that they would continue beyond the duration of the study. Per person programmatic costs will be calculated by dividing the total costs of the program by the total number of children with persistent asthma in the schools. We will determine *productivity/opportunity costs* based on the amount of time parents take from work to care for sick children or take them to a doctor. Time from work will be valued at the median of the pay scale estimates based on age, race and gender specific wages from the Bureau of Labor Statistics. We will assess the impact of the intervention on *medical* costs using parent-reported health services use data and medical record review. We will ask parents at each follow-up about their child's ER or physician visits, hospitalizations, medical procedures, use of medications and durable equipment. Healthcare use will be converted to costs using the NYS Medicaid fee schedule and other sources. Annual medical costs per person will be analyzed using a 2-part model to adjust for zero expenses in a given year. All costs will be adjusted to the last year of the intervention using the appropriate component of the Consumer Price Index (CPI).

We will consider the total costs of initiating and maintaining the program as well as the incremental cost-effectiveness ratio (ICER) of the SB-TEAM vs. eUC, which is the ratio of differences in costs between the 2 study groups to the difference in the number of symptom-free days (SFD) gained between the 2 groups. The main outcome for the analysis from the societal perspective will be an incremental cost-effectiveness ratio (ICER), which is the ratio of net program costs to the number of symptom-free days (SFD) gained, $ICER=(\Delta Medical+\Delta Productivity+\$Program)/\Delta SFD$, where $\Delta=(SB\text{-}TEAM)-(eUC)$. We will bootstrap the ICER to estimate standard error and to evaluate the uncertainty around the point estimate. The ICER will be compared to similar estimates from the literature. An acceptability curve, linking various values of 1 SFD to the probability of SB-TEAM being cost-effective, will be plotted. The study from the Medicaid perspective will use the cost-benefit approach to economic evaluation. Benefits will be described as the net difference in medical and productivity costs between children in the SB-TEAM and eUC groups. The cost is equivalent to the cost of the program. Equation: $Net\ Monetary\ Benefit=\Delta Medical-\$Program$.

Process Evaluation: Descriptive statistics will be used for the process evaluation, looking in particular at the efficiency of the program implementation along with the responses from parents, primary care providers, and school nurses and administrators about convenience, scheduling, satisfaction, and sustainability.