School Based Asthma Care for Teens (SB-ACT):
A Randomized Control Trial to Improve Preventive Asthma Care for Urban Adolescents

Investigators:

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Background:

Asthma is the most common chronic illness of childhood,[1,2] affecting more than 10% of children in the city of Rochester. Despite current advances in asthma therapies, morbidity and mortality continue to increase. While evidence-based national guidelines recommend effective preventive medications for all children with moderate to severe asthma,[3,4] studies indicate that many children in the U.S. who should receive preventive medications are not receiving them.[5-7]

Low-income, minority teenagers have disproportionately high rates of asthma morbidity, including excess risk of emergency department care, hospitalization, and death from asthma, compared to white adolescents.[8,9] Although urban children suffer the largest burden from asthma, they are the least likely group to receive adequate preventive care,[10,11] and this poor adherence plays a significant contributing role in asthma morbidity. Inner city adolescents with asthma are at particular risk of non-adherence. Thus, there is a substantial amount of suffering that could be prevented with improvements in care.

Preventive medicines for asthma, if used properly, reduce symptom and prevent asthma hospitalizations.[12] Current national guidelines specifically recommend the use of these evidence-based daily preventive medications for all children with persistent asthma.[4] However, many children in the U.S. and in Rochester who should receive these medications are not receiving them.[5-7] We found that 74% of children nationally with significant asthma symptoms were not receiving daily preventive medications for asthma.

Adolescents, as a group, tend to have poorer medication adherence than younger children or adults. Early adolescence is a developmental period that involves changes in cognitive processes, social influences, and biological factors that may be significant contributors to the decrease in medication adherence seen in this age group. During early adolescence, parents typically grant their child increased independence and responsibilities. When the child has a chronic illness, age 7-8 years is the time that parents often begin the transition of responsibility for illness management from parent to child, and by age 15 the child typically assumes more responsibility than the parent for day-to-day management tasks. This transition in responsibility is often marked by decreased adherence.[10] Not surprisingly, poor adherence is associated with worse disease-related outcomes.

The goal of this study is to evaluate the widespread implementation of a developmentally appropriate preventive asthma care intervention for urban teens. The School Based Asthma Care for Teens (SB-ACT) program includes two core components: 1) a trial of directly observed therapy (DOT) to allow the teen to experience the potential benefits from adhering to guideline-based asthma treatment, and 2) a developmentally appropriate Motivational Interviewing (MI) Counseling Intervention to help the teen transition to independent long-term medication adherence. We hypothesize that teens receiving the SB-ACT program will 1) experience less asthma-related morbidity than the asthma education (AE) attention-control comparison group,

and 2) have improved adherence, less urgent healthcare use, less absenteeism, improved quality of life, and reduced FeNO compared to AE. We also hypothesize that participants receiving DOT-only will have improved asthma-related outcomes immediately following their DOT trial vs. teens receiving AE, but will not have sustained, clinically significant improvement in outcomes once the DOT phase is complete. This represents a unique opportunity to build upon existing community relationships with an innovative and developmentally focused program to improve asthma outcomes for urban teens.

Study Objectives:

This study has the following objectives:

1. To identify and recruit an urban sample of adolescents (12-16 year olds) with mild persistent to severe persistent asthma from approximately 30 schools throughout the Rochester City School District and surrounding school districts.
2. To enroll subjects into a 3-group randomized trial of the School-Based Asthma Care for Teens (SB-ACT) program; 1) the SB-ACT program, which includes a 6-8 week trial of DOT plus 3 MI counseling sessions; 2) DOT-only (6-8 week grail of DOT alone); and 3) an asthma education (AE) attention-control comparison group.
3. To collect baseline morbidity data to characterize this group of teens with asthma and determine risk factors for the frequency and severity of recurrent symptoms.
4. To follow these subjects prospectively through the year following enrollment for clinical outcomes (symptom severity, health care use, exhaled nitric oxide) and functional outcomes (functional limitations, school absenteeism, quality of life).
5. To assess the effectiveness of the SB-ACT intervention in reducing asthma morbidity.
6. To explore potential mediators (motivation, confidence, and beliefs about medication) and moderators (demographics, depressed mood, school/neighborhood variables) of the intervention effect.
7. To perform an economic sustainability analysis (health and economic benefits of SB-ACT, DOT-only and AE using cost-effectiveness methodology).
8. To evaluate the process of program implementation using RE-AIM metrics.

Study Overview:

A. Study Design

We propose a 3-group randomized trial of the School-Based Asthma Care for Teens (SB-ACT) program. 430 teens with persistent asthma will be randomized to either: 1) the SB-ACT program, which includes a 6-8 week trial of DOT plus 3 MI counseling sessions; 2) DOT-only (6-8 week trial of DOT alone); and 3) an Asthma Education (AE) attention-control comparison group. Families and teens will be followed prospectively for one calendar year, with systematic assessments completed at 3-, 5-, 7-, and 12-months post-enrollment.

B. Subjects and Setting

Adolescents 12-16 years of age attending secondary school in the Rochester City School District (RCSD) and surrounding school districts will be screened for eligibility at the start of the school year. A total of 430 teens will be recruited over 4 years from approximately 20 schools. School-based screening, used successfully in our past programs, will identify teens for the program. In compliance with the Family Education Rights and Privacy Act, our study has access to the RCSD medical alert forms that include whether or not the teen has a breathing problem. For the surrounding school districts, school nurses or administrators will contact caregivers of potentially eligible families, and if the family is interested, will connect the caregiver with the study team for an eligibility assessment. Additionally, we will review potentially eligible teens from Dr. Halterman's Future Contact Database (RSRB# 31010) to inquire if prior study participants are eligible and interested in the current study. We will assess

eligibility for the study by a telephone survey with the primary caregiver.

Eligibility requirements include:

1) Physician-diagnosed asthma (based on caregiver report).
2) Persistent asthma severity or poor asthma control (based on national guidelines[4] and caregiver report). Per NHLBI EPR-3 criteria, any 1 of the following:
   a. In past month, >2 days/week with daytime asthma symptoms
   b. In past month, >2 days/week with rescue medication use
   c. In past month, >2 times/month with nighttime awakening due to asthma symptoms
   d. ≥2 asthma exacerbations during past year that required oral systemic corticosteroids
3) Age ≥12 and ≤16 years
4) Attending secondary school in the Rochester City School District or surrounding school districts.

Exclusion Criteria:

1) Inability to speak and understand English.
2) No access to a working phone for follow-up surveys (either at home or an accessible alternate location).
3) Diagnosed developmental or intellectual disability.
4) Other significant medical conditions, including congenital heart disease, cystic fibrosis, or other chronic lung disease, that could interfere with the assessment of asthma-related outcome measures.
5) Teens in foster care or other situations in which consent cannot be obtained from a legal guardian.

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

C. Study Procedures

1. Screening procedures

Screening will occur from late summer (as soon as school enrollment forms are available to the team) until the end of January (since new screening information becomes available during the first few months of school). To evaluate subjects for eligibility, screening procedures occur up to 4 weeks prior to the baseline assessment and randomization. The baseline assessment includes symptom questions to be assessed for all teens and will be reviewed for teens that we are unable to complete the baseline within 4 weeks of the screening survey.

We will identify teens through school "medical-alert" forms that include whether or not the child has a breathing problem or referral from school nurse. All teens who have a breathing problem indicated on their medical-alert forms will be identified. We will conduct a telephone screening survey with the caregiver to assess eligibility, and only teens with persistent symptoms or poor asthma control will be eligible. Enrollment and randomization occur in a rolling fashion from the first day of school until the end of February (since enrollment can occur up to 4 weeks after screening survey completion).

2. Baseline

Home visits will be used to explain the study, elicit informed consent from the parent and assent from the teen, and obtain baseline measurements. Baseline evaluations include: confirmation of inclusion/exclusion criteria, assessment of baseline severity, collection of demographic and health history variables, measurement of pulmonary function (using a

portable spirometer), exhaled nitric oxide (FeNO – for airway inflammation), salivary cotinine, height, and weight. All surveys questions will be read aloud to caregivers and teens. We will give a symptom diary to the teen and caregiver for symptom tracking, assist in finding a prominent location for it, and review its use. For home interviews in which the child is not present, we will determine another time to come to the home to obtain the teen's assent, conduct the baseline surveys, and collect samples and measurements. If it becomes difficult to reach the child at home we will ask the parent's permission to meet with the child at the school nurse's office to obtain assent, and collect the cotinine, FeNO, spirometry, and height and weight measurements. We will then contact the child by phone to complete the baseline survey. *(Note: If teen refuses to assent to the study, the study subject will be withdrawn and all study materials will be destroyed.)*

We will use portable spirometers and FeNO machines to measure the teen's pulmonary function and airway inflammation. Some teens may have difficulty with these procedures; we will only include data for teens able to perform the procedures accurately. We will use a portable scale and stadiometer to take objective measurements for height and weight.

Exposure to Secondhand Smoke will be assessed by both interview survey and cotinine measurements. A member of the research team will collect salivary fluid samples from each child using a small sterile swab. Collection will be made according to a standard protocol developed for use with children and adolescents. Salivary samples will be stored frozen and shipped via courier to Salimetrics, LLC in State College, PA for analysis. The Environmental Assessment will include a survey inquiring about environmental exposures and an observation checklist that a member of the study team will perform.

3. Randomization

Following the baseline assessment, each teen will be randomly assigned to one of 3 groups: 1) the SB-ACT program, which includes a trial of DOT plus a self-management MI counseling intervention; 2) DOT-only; or 3) an asthma education (AE) comparison group. *Randomization will be stratified by school and preventive medication at baseline*. Since enrollment will occur over a period of 1-5 months at the start of the school year, a permuted block design will be used to assure approximately equal allocation of teens in each group over time. The randomization scheme will be independently developed by a programmer in the Biostatistics Center. After baseline completion, the interviewer will call the study coordinator who will provide the subject's ID number and treatment assignment.

4. SB-ACT Intervention:

School Nurse Assisted Preventive Medication Use (Directly Observed Therapy)

We will communicate with the child's healthcare provider about the child's symptoms and if child is not already taking a preventive medication, to determine an appropriate preventive medication for the teen. We will facilitate the child receiving their preventive medication at school. If needed, new prescriptions will be sent to pharmacies for parent pick-up or delivery (several local pharmacies provide delivery services) with instructions indicating one canister of preventive medication to be dispensed for the home and a second canister for the teen's school. This system has been successfully implemented in our prior studies. The school nurse and teen will meet at the beginning of the program to develop an individualized plan for the timing of DOT in the school to avoid disruption of classes and allow the teen choice in this process. For the first 6-8 weeks after enrollment the teen will visit the school nurse once a day to receive a daily dose of preventive asthma medication. Study personnel will review the DOT protocol and proper administration technique with the school nurse. The purpose of this intervention component is for teens to establish a relationship with the school nurse, learn proper medication technique, and experience potential benefits of consistent

preventive therapy. As in our prior studies, most teens will receive once daily dosing since it is effective and allows for administration of medication during school hours; if more frequent dosing is needed additional doses will be taken at home. The teen will use his/her home inhaler for doses on weekend days and other days in which he/she does not attend school.

While many schools do not have a full time nurse, all schools are prepared for medication administration as many teens have daily medication needs (e.g., medications for attention deficit disorder). In our prior study, medications were administered >95% of the time the teen was in school, even in schools with only part-time nurse coverage (the majority of schools). All teens will be instructed to rinse their mouth with water after each medication dose. A medication dispensing log will be used for tracking purposes, and contacts with the nurse will be tracked. While adherence will be assured by the nurse on the days the teen attends school, adherence will simply be encouraged on days the teen does not attend school. Guideline-based medication adjustments ('step-up') will be recommended to the child's provider after the first follow-up if persistent symptoms continue.

Since the goal of SB-ACT is to ultimately support the teen's transition to independent, sustained use of preventive medications, MI counseling, the second component of the intervention, will start 4-6 weeks after the commencement of DOT. A brief survey tool will be administered by the school nurse weekly, following the first 6 weeks of DOT, to help determine collaboratively with the teen if they are ready to transition to independent medication use. The teen will report their motivation to use preventive medications independently (1-10 scale, 'readiness' = score $\geq$8), their confidence in adhering to the treatment plan, and whether they have obtained needed refill medications for ongoing use.[13] While the goal of the counseling sessions is to help the teen move towards autonomy with medications, some teens may request to continue DOT for a longer time period. We deliberately provide this choice to support teens' autonomy in decision-making, which is appropriate for this developmental stage. We will track any contacts with the school nurse throughout the school year.

Motivational Interviewing (MI) to Transition the Teen to Independent Use of Preventive Medications:

This intervention component consists of an evidence-based self-management program to help the teen begin to transition to independence with preventive medication use. A trained community nurse or counselor will conduct three in-person MI sessions with the teen at school to enhance the teen's motivation to adhere to their guideline-based asthma treatment plan (developed during the DOT phase). All sessions will take place in a quiet location at a mutually agreed upon time that limits interference with classes and activities. The three sessions consist of an initial 40 minute counseling session (4-6 weeks after start of DOT), and two 30 minute follow-up sessions 2 and 6 weeks later. The teens will also have the option of calling the nurse for reinforcement after the 3rd session if they desire additional support. We will systematically track the number and length of contacts.

a. Initial MI visit

The focus of this intervention component is to build motivation for and to resolve ambivalence regarding asthma medication adherence. Within the context of MI counseling delivery, asthma education (based on the same content used for the AE group) will be provided in a non-prescriptive manner using the MI technique of "elicit-provide-elicit".[14] The counselor will first elicit the teen's knowledge about the importance and health effects of proper medication adherence. The counselor then will offer recommendations in a non-confrontational manner that supports and

respects the teen's autonomous decision-making. Teen-endorsed goal setting, problem solving and other behavior change strategies will be utilized. This approach does not regard the teen as a passive recipient of information, but rather an active collaborator in the change process. Using MI, the counselor will use open-ended questions and reflections to explore the teen's ambivalence towards taking medications (e.g., pros and cons). The counselor will empathize with the teen's struggles, elicit concerns about changing and not changing medication taking behavior, and explore ways for the teen to communicate their needs (e.g., with the PCP). The teen will be encouraged to reflect on his/her experience with DOT in school, and the benefits gained from taking medicines consistently. The counselor will inquire about things the teen feels are important (values, goals, interests), and where appropriate address discrepancies between the teen's current behaviors (e.g., not taking medicine) and goals (e.g., being on basketball team).

The MI sessions are targeted towards the adolescent. However, we recognize that the caregiver can provide valuable information about the impact the teen's asthma has on the teen and the family. It will be important, particularly when the parent maintains significant influence over the teen's asthma management (e.g., getting medications/refills), for caregivers to provide input and consensus with the change plan that is developed. The counselor will call the caregiver following each session. Using MI-compatible strategies, he/she will assess asthma control from the caregiver perspective, and the caregiver's role in supporting or hindering the teen's asthma self-management.

b. Follow-up MI sessions

Follow-up sessions will occur approximately 2 and 6 weeks following the initial session. These sessions will focus on understanding the teen's perspectives and choices regarding asthma management, offering continued support for autonomous decision making around medication adherence, discussing barriers to independent adherence, and identifying any benefits associated with ongoing preventive asthma care. The teens will be asked about any anticipated obstacles (e.g., getting medication refills, making a follow-up visit with the provider). If the teen is not using preventive medications daily, the nurse will continue to explore ambivalence and address discrepancies between the teen's behavior and his/her current goals.

Supervision of MI sessions will be provided by an investigator (B. Borrelli) and coordinator to assure fidelity to the MI intervention; all sessions will be audiotaped and a minimum of 20% will be reviewed.

5. DOT-Only Group:

As with the teens in the combined SB-ACT group, we will communicate with the child's provider of those in the DOT-only group to assure each teen has preventive medications at home and school. Teens in the DOT-only group will receive a trial of 6-8 weeks of directly observed administration of preventive asthma medications from the school nurse (with dose-adjustments as needed), but will not receive MI counseling. The school nurse will use the same survey tool as for the SB-ACT group to help determine with the teen if they are ready to transition to independent medication use, and will encourage the teen to reflect on their experience using these medications. As in the SB-ACT group, teens may ask the nurse to continue DOT beyond the initial trial period; contacts will be tracked. Outcomes from this group will help determine whether a trial of DOT alone is sufficient to promote sustained adherence and reduced morbidity.

SB-ACT and DOT-Only: 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.

6. Asthma Education (AE) Comparison Group:

We will notify the teen's healthcare provider that teens in the AE group have persistent asthma symptoms that warrant use of effective guideline-based preventive medications. We also will provide an in-school asthma education program,[15] provided by community asthma educators or nurses. The program will include asthma management instruction and will be geared toward teens living in underserved neighborhoods. The program will match the time and attention of the MI counseling portion of SB-ACT. Sessions will be delivered at school by a trained health educator, in a similar structure and time-schedule to the MI intervention (i.e., each teen will receive three 1-on-1 educational sessions at school). Sessions will cover 3 main topics: 1) lung physiology and asthma basics, 2) triggers, symptoms, and warning signs, and 3) medications and self-advocacy. As in SB-ACT, caregivers will be called after each session to reinforce key points and answer questions. Bi-monthly supervision will be provided by the PI and research coordinator to assure fidelity to the AE intervention; all sessions will be audiotaped and 20% will be reviewed.

Teens will not be blinded to group allocation; they will be told they are randomly assigned to different ways of approaching asthma management. As in our prior work, to avoid differential attrition we assure sessions are interactive and provide flexible scheduling and reminders.

7. Asthma Control Status at Follow-Up

Criteria for a preventive medication adjustment recommendation at the 3 month Follow-Up assessment for the DOT-only and SB-ACT treatment groups:

1. **<u>Caregiver 3mo. FU</u>**; ***one (or both) below evidencing poor control status***:
    - **a.** NHLBI criteria
    - **b.** ACT score ≤ 19

<u>AND</u>

2. **<u>Teen 3mo. FU</u>; *one (or both) below evidencing poor control status:***
    - **a.** NHLBI criteria
    - **b.** ACT score ≤ 19

<u>AND</u>

3. **Caregiver and/or teen reports making any effort to take/continue the prescribed preventive medication at school/home**

If the above conditions hold true, a step-up adjustment recommendation (and/or a change to once daily dosing) will be made. This will happen regardless of whether school DOT is continuing or the teen has already transitioned to independent use.

Medication Adjustment Procedure: Generate a NHLBI symptom report to justify a preventive medication action and draft a prescription recommendation for PCP to consider and authorize (possibly with edits). After receipt of PCP decision, caregiver will be contacted to explain recommendation and obtain consent. Submit new prescription to pharmacy and deliver

to school/home as needed. If medication adjustment is NOT agreed to by caregiver then notify PCP of decision not to adjust.

Note: If caregiver and teen both report NO attempt to be adherent and asthma control is poor then Asthma Care Coordinator will encourage caregiver/teen to restart the previously prescribed preventive medication and no adjustment recommendation will be initiated.

For AE-only subjects who meet the criteria above: Send caregiver a poor control follow-up notification letter encouraging family to pursue preventive asthma care due to teen's continuing persistent symptoms. Send PCP a notification letter calling attention to teen's continuing persistent symptoms.

8. Participant Follow-up

Outcome measures will be assessed at 3, 5, 7 and 12 months after baseline for all subjects by an independent group blinded to treatment allocation. We will use structured telephone interviews with both the teen and caregiver for follow-up surveys. We may also send reminders and schedule appointments through text messages and emails. Text messages will be formatted in a manner that provides research relevance in the absence of personal health information (PHI). We may use a limited data set when sending text messages that can include dates and times for visits or telephone call reminders. FeNO, spirometry, cotinine, height, weight and adherence measurements will be conducted through home or school visits at specific time-points (see below). Medical record review also will be performed.

Measures *(see below for Measurement Table with scales and timing of administration)*

Symptom Severity:

a) The primary outcome measure will be the number of symptom-free days (SFDs) at the 3, 5, and 7 mo. follow-ups. This outcome measure is consistent with the symptom monitoring suggested by the national guidelines,[16] and we collected prospective data on SFDs in our prior studies, enabling a realistic calculation of sample size requirements. At each follow-up, parents and teens will report the number of days the teen experienced no symptoms of asthma (defined as 24 hrs with no coughing, wheezing, shortness of breath, and no need for rescue medicine) in the past 2 weeks. Symptom diaries will assist with recollection.

b) Secondary measures: Parents and teens will be asked to report the number of "steroid bursts" for asthma, as well as urgent (ED visits, hospitalizations, school exacerbations requiring treatment) and non-urgent (primary and specialist care) visits. With parent permission, we can access charts at each medical practice and will review medical records to verify visits. We also will measure the number of nights with asthma symptoms, days needing rescue medications, days with limited activity, and asthma control with the asthma control test (ACT).[17,18]

Adherence: We will use Horne's adherence scale,[19] and also will ask teens to report doses missed in the prior 2 weeks. To provide objective adherence data for teens in each group, we will monitor dose counters that are integrated into medication canisters. Almost all inhaled steroids now include counters, and in our prior study 99% of children used medication that included integrated counters. At baseline, 5-months, and 7-months, we will use home visits to document the number of doses on the teens' preventive medication inhaler (or count remaining pills for oral medications, i.e.; Singulair), and return 2 weeks later to re-measure the doses used. Based on the prescribed regimen, we will calculate adherence (#actuations / #prescribed) over the prior 2 wks. For teens in the SB-ACT and DOT-only groups, we will also collect school medication administration logs and will record the time to transition to independent medicine use.

Functional Outcomes and Services Utilization: We will measure adolescent and caregiver quality of life using the Pediatric Asthma Quality-of-Life Questionnaire and the Pediatric Asthma Caregiver's Quality of Life Questionnaire.[20,21] School absenteeism will be assessed by teen/caregiver report and school records, and we will assess caregiver's workdays missed for teen's medical visits or illness. We will also assess other utilization, caregiver time costs, and out-of-pocket expenses (e.g., visits to the nurse's office for exacerbations, loss of activities, urgent care utilization, medication costs, visit co-pays, and transportation costs).

Airway Inflammation: We will obtain exhaled nitric oxide (FeNO) measurements at baseline, 5 month follow-up, and 7-month follow-up. We will use a NIOX VERO Airway Inflammation Monitor; a portable device that measures FeNO using the electrochemistry method (range 5-300ppb). Teens exhale into the device for 10 seconds. FeNO is elevated in inflammatory diseases and decreases with inhaled steroid treatment.[22]

Pulmonary function: At baseline, 5 month follow-up, 7-monthfollow-up teens will blow into a portable spirometer to assess lung function.

Height & Weight: At baseline, 5, month, 7 month follow-up, a portable scale and stadiometer will be used to take objective measurement of the teen's height and weight.

Independent Variables/Potential Moderators: We will collect caregiver-reported measures of demographic, personal, and community factors known to be associated with asthma morbidity in high risk children or influence response to interventions. These include demographics age,[7,23] race/ethnicity,[5,24,25] gender, insurance,[5,7,26] caregiver's education[7], and caregiver and teen-reported depressed mood,[27,28] using the Center for Epidemiologic Studies-Depression Scale[29] and the Center for Epidemiological Studies Depression Scale for Children.[30,31] Since smoke exposure is associated with asthma morbidity,[32,33] we will measure teens' salivary cotinine levels (baseline, final).[34,35] For school/community variables, we use the Neighborhood Social Cohesion scale,[36] school size, graduation rate, % free/reduced price lunch, and racial composition.

Potential Mediators: To explore potential mediators related to the conceptual model, we will use a Motivation and a Confidence Rating[37] to assess teens' motivation to improve their asthma medication use, and the teens' perceived confidence in "how sure they are that they can take their medication every day," (scale 1-10). We will measure beliefs using the Beliefs about Medications Questionnaire.[38] The Beliefs About Medication Scale - Intent to Adhere Subscale (BAMS-IA)[39] will assess the teens' intention to adhere to their medication regimen independently during the subsequent two weeks. The Asthma Readiness to Change Questionnaire[40] will assess readiness to change their medication use. We also will use the Health Care Climate Questionnaire[41-43] to assess the teen's relationship with the school and MI nurses and health educators.

9. Measures

The table on the following page summarizes the use of all instruments used for this study including how the data is collected and the times of administration.

Outcomes	Measurement Strategy	Time of Administration
Symptom Severity	Teen and caregiver report, NHLBI guideline-based items Asthma Control Test (ACT)	Baseline, each follow-up
Airway Inflammation	Objective Measurement: FeNO	Baseline, 5 months, 7-month,
Lung Function	Objective Measurement: Spirometry	Baseline, 5 months, 7-month,

Height and Weight	Objective Measurement: Scale, Stadiometer	Baseline, 5 months, 7-month,
Medication Adherence	Teen and caregiver report, Horne adherence scale Objective Measurement: Monitoring of integrated medication counters	Baseline, each follow-up Baseline, 5 months, 7-month,
Functional Outcomes and Service Utilization		
Quality of Life	Teen – Juniper PAQLQ Caregiver – Juniper PACQLQ	Baseline, each follow-up
School Absenteeism	Teen and caregiver interview School record review	Baseline, each follow-up
Health Care Utilization	Teen and caregiver interview Medical record review	Baseline, each follow-up
Additional Cost Measures	Caregiver interview (caregiver missed work, out of pocket expenses, transportation costs, etc.)	Baseline, each follow-up
Independent Variables		
Demographic, Medical Variables	Teen and caregiver interview	Baseline
Depressed Mood*	Caregiver – CES-D Teen – CES-DC	Baseline, 7- month Baseline, 7- month
Secondhand Smoke	Teen and caregiver interview Objective Measurement: Salivary Cotinine	Baseline, each follow-up Baseline, 7-month
Potential Mediators		
Motivation	Teen - Medication Adherence *Motivation* and *Confidence*	Baseline, each follow-up
Beliefs about Medications	Teen and caregiver – Beliefs about Medications Questionnaire (BMQ) Teen – Beliefs About Medications – Intent to Adhere Subscale (BAMS-IA), Asthma Readiness to Change Questionnaire	Baseline, 7-month Baseline, 7-month
Process Evaluation		
RE-AIM Summary Measures **See detailed table in Process Evaluation section below**	RE-AIM Dimensions and Questions for Evaluating Health Education and Health Behavior Research	At end of each study year

* Parents and teens whose scores indicate they may be suffering from mild to severe depression will be provided a list of mental health services and providers in the community, and will be referred to their primary care provider.

10. Compensation

Teens and caregivers will each receive a $20 gift card following baseline survey, $10 after the 3- and 5- month follow-ups, and $30 after the 7- and 12- month follow-ups. Payment to participants will be in the form of a prepaid Visa debit card from Bank of America. The use of these cards allows for tracking the use of lost or stolen cards and provides flexible options for participant use.

11. Process Evaluation

We will consider both individual and institutional level impacts and resources available in 'real world' schools and communities. We will use ***RE-AIM***[44] metrics to assess :*1)* the

proportion of eligible subjects who participate and the representativeness of participants compared to non-participants (*Reach*), *2)* the intervention's impact on primary outcomes and quality of life *(Effectiveness), 3)* characteristics of schools and program support by school administration, nurses, providers, and teens/caregivers *(Adoption), 4*) the consistency in delivery of each intervention component (including the efficiency of the delivery of medication to the schools, the % of days teens receive medications in school, % completed counseling sessions, and whether additional contacts with the nurses occur beyond the intervention period) (*Implementation*), and *5)* the extent to which intervention components continued or were modified post-study completion and its long-term effects *(Maintenance).* The final interview will also include Likert-scale and open-ended questions to teens, parents, PCPs, school nurses and administrators about convenience, scheduling, and satisfaction.

RE-AIM METRICS		
RE-AIM	**QUESTIONS**	**ASSESSMENT METHOD**
Reach (Individual Level)	What percent of eligible participants: a) were excluded, b) took part and c) how representative were they?	Response rate and demographics
Effectiveness (Individual Level)	Effect of intervention on primary outcomes and QOL? Were pre-determined NHLBI guideline-based targets achieved?	Primary analysis (symptoms, quality of life; economic evaluation)
Adoption (Setting/Staff Level)	Characteristics of participating secondary schools, time and resource burden on school and community personnel.	School characteristics, demographics, staff surveys
Implementation (Setting Level)	To what extent were the various intervention components delivered as intended by school and community staff members?	Medication delivery log, session completion rate, contacts with nurses, surveys
Maintenance (Individual Level)	Long term effects at 12 months? Attrition rate? Were drop-outs representative; how did attrition impact conclusions?	Analysis of long-term outcomes (12 month assessment), attrition, demographics
Maintenance (Setting Level)	a)To what extent were intervention components continued post-study completion, b)how was the program modified	Survey and semi-structured interviews with school nurses, administrators, ALA leadership

12. 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 locked in an office or filing cabinet and will only be accessible by the study staff.

Baseline, follow-up, and chart review data will be entered into a password-protected 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 and stored using RedCap, a secure, password protected database (using University NetID's and passwords) hosted through the University of Rochester.

The counseling and education sessions will be audio recorded. These recordings will be saved on Box.net, a secure and University supported database that will only accessible by investigators and study personnel. These recordings will be used for supervision of the counseling and education sessions to ensure the protocol is being followed correctly.

Portions of the final assessments with caregivers, nurses, and healthcare providers may be tape recorded too. 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.
For surrounding school districts, the study team will not have access to student data until the family has consented to the study procedures.

13. Safety

This is ***not*** a drug investigational study since the effectiveness and safety of the drugs are not being tested. The randomized trial proposed will pose minimal risk to the teens, since the medications used by the teens (and delivered at school for the teens in the SB-ACT and DOT-only groups) are FDA approved preventive medications that are recommended as the standard of care[45] for children and adolescents with the degree of symptom severity required for enrollment into the program. 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. Any significant concerns will be relayed promptly to the study coordinator, the principal investigator, the teen's health care provider, the Institutional Review Board, the DSMB and the NIH. There is a potential risk of adverse effects on linear growth from the use of inhaled steroids;[46] however, this risk is felt to be outweighed by the benefits for children and adolescents with persistent asthma. In general, these medications are well tolerated and safe. Health care providers will prescribe all medications and will follow the teen for any potential side effects and monitor the teen's growth during the course of the study.

The frequency and severity of all reported adverse events will be systematically recorded. Telephone interviewers will inquire about any adverse events, and specifically ask about any yeast infections of the mouth and facial rash. Any teen experiencing an acute asthma exacerbation at the time of a home visit or follow-up phone call will be referred immediately to their health care provider for care, and their caregiver will be notified. In addition, school nurses will be instructed to contact the caregiver of any teen presenting to the nurses office with acute symptoms and refer them promptly to their health care provider.

There is a risk that the study team may discover an unknown medical condition. If this is to occur, we will refer the family to their health care provider or another appropriate health care professional for evaluation and treatment.

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.

14. Data and Safety Monitoring

Data Quality Monitoring

Principal investigator, Dr. Halterman, will take responsibility that the study is adequately monitored and that the data are secure. Co-investigators, Dr. Borrelli and Dr. Riekert each have human subject protection certifications through their institutions. All UofR recruitment staff will have human subject protection certifications prior to recruiting subjects into the study and will be included in the IRB application. Recruitment will only occur at the University of Rochester. There will be no enrollment of subjects at the University of Boston Medical Center or Johns Hopkins University.

Research assistants/interviewers will be responsible for all assessments, and will receive training from key study personnel regarding asthma terminology, symptoms, and medication understanding. They will be trained by the study coordinator on the use of the spirometer, FeNO machine, scale, stadiometer, and salivary collection methods.

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.

Once forms have been collected, errors that can be corrected over the telephone (legibility, incorrect dates, etc.) will be done using telephone interviews with the parents. 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 (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 information analysts for accuracy. Required regulatory documents (IRB approval, updates to the protocol, data monitoring documents) will be maintained by the study coordinator. All events during the course of the trial including study enrollments, adverse events and study terminations will be reported to the study coordinator (see Safety Monitoring section below).

Safety Monitoring

A Data Safety Monitoring Board (DSMB) including a pediatric allergy and immunology specialist (Tamara Perry, MD; Arkansas Children's Hospital Research Institute), an epidemiologist (Susan Fisher, MS, PhD; Temple 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 health 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.

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

15. Potential Benefits

Adolescents may or may not benefit from the study. They may experience improved asthma morbidity due to the additional time and attention they receive around their asthma and asthma care. Additionally, teens in the groups receiving preventive medications may experience reduced symptoms due to taking their medication daily. In addition, the teen's health care provider will be alerted of their asthma severity, and families will receive telephone calls in order to assess the teen's ongoing symptoms. It is possible that an increased awareness of symptoms and enhanced communication with the health care provider will occur, and will result in improved asthma care and reduced morbidity for these adolescents.

16. Analysis

Sample Size and Power Justification:

This study is designed to have adequate power to test the primary hypothesis that teens receiving SB-ACT will have more symptom-free days at the 3, 5, and 7 -month evaluations compared to AE. Previous asthma interventions, including the SBAT trial, have demonstrated that improvements of 0.9 SFD/2 weeks are feasible and clinically meaningful.[47,48] Based on our prior data, we estimate a pooled standard deviation (SD) of SFD to be 2.6 and within-subject correlation (ICC) of 0.3-0.4. We calculated power for the intervention effect on SFD while justifying repeated assessments for outcomes (5, 7, 12 months). A sample size of 123 subjects per group will obtain 94-96% power to detect a difference of 0.9 in SFD at a two-sided 5% significance level (assuming ICC: 0.3-0.4). We anticipate <15% attrition, as attrition was minimal (<5%) in the prior study, and therefore plan to enroll 430 teens. To test the short term intervention effect of DOT-only vs. AE, the sample size of 123 per group will obtain 80% power to detect a difference of 0.93/2 weeks at 3-month assessment with a two-sided 5% significance. We expect the DOT-only intervention won't sustain the effect at long term follow-up compared with AE. To test this, the proposed sample size will have 86% power at a one-sided 5% significance level, using a non-inferiority test with a margin of equivalence of 0.9 and a SD of 2.6. To compare the long-term effect of DOT-only vs. SB-ACT, we will have 80% power to detect an effect size of 0.4 at a two-sided 5% significance level.

To evaluate the intervention effect ***within*** each study arm, we anticipate in the SB-ACT group the rate of asthma control, asthma exacerbation and no absences will reach a guideline-based target of 80%. 123 subjects will have 80% power to claim a rate $\geq$80% with a non-inferiority margin to be 10%, at a one-sided significance level of 5%.

There are 10,900 teens in 7th-10th grade in the city school district and >6,000 entering 7th graders in a 3 yr. period. Conservatively assuming an asthma prevalence of 10%,[1] >1,690 of these students have asthma, and approximately ½ have persistent asthma. In our prior study, we enrolled 74% of eligible subjects. We can conservatively enroll 126 subjects/year (60%); which is more than adequate for sample size requirements.

Primary Analysis:

We will use graphs and descriptive statistics to summarize outcomes by intervention group at each time point. We will assess for differences between groups at baseline despite randomization (e.g., demographics, depressed mood, school/neighborhood factors) to enable the identification of covariates to be controlled in later analyses. If distributional

assumptions associated with a particular statistical procedure are violated, we will use appropriate transformations or non-parametric alternatives. Analysis will be performed under the intent-to-treat principle.[49] Hypothesis-driven comparisons will be made to control the family-wise type I error rate at 0.05 (2-sided) for primary hypotheses.

We expect minimal loss to follow-up.[13,47,50] Inferences are valid if missing data follows the missing completely at random (MCAR) assumption.[51] However, the occurrence of missing data may depend on the observed response, thus we will perform sensitivity analysis to examine the MCAR assumption. If it is severely violated, we will report treatment effects using weighted GEE to address MCAR. Biased estimates may also arise in the case of non-ignorable non-response (NINR). Although unanticipated, we will examine NINR using the joint modeling approach.[52] For SEM, the maximum likelihood estimates (MLE) are valid under MAR, if the posited distribution models are satisfied. In the presence of missing data, estimates from LMM and SEM may be biased if parametric assumptions are not met, even with the use of robust variance estimates. If this arises, we will change the distribution models and/or use clustered bootstrap methods for inference.[53]

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