PROTOCOL TITLE:

Using Technology- Assisted Stepped Care Intervention to Improve Adherence in Adolescents with Asthma

PRINCIPAL INVESTIGATOR:

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	6/4/2019	The data safety monitoring plan was added to the appendix of the protocol. In addition, a reference was added.	Yes
2	8/7/2019	Language about participants being paid during the Step 2 intervention was added. Information about when the CEQ questionnaire was completed was edited. Finally, the Perceived Characteristics of Intervention Scale was added.	Yes
3	10/17/19	The time period for baseline was extended to 2 months. One exclusionary criteria item was added.	Yes
4	3/18/2020	Information about the measures and procedures completed during recruitment and at the baseline visit was adapted to allow for remote visits.	No
5	4/2/2020	Study procedures for the telehealth sessions were revised to allow for food delivery.	No
6	5/22/2020	Electronic consent was modified to allow for the use of REDCap.	No
7	12/09/2020	A short questionnaire was added with questions regarding how COVID-19 has impacted learning.	No
8	11/23/2022	Protocol was updated to include a new company that will be providing inhaler sensor caps. In addition, the name of a specific asthma management app was made generic.	No

9	8/16/2023	Protocol was updated to change sample size from 70 to 80 participants	No

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1.0 Study Summary

Study Title	Using Technology- Assisted Stepped Care Intervention to Improve Adherence in Adolescents with Asthma
Study Design	Randomized Controlled Trial
Primary Objective	To test the preliminary efficacy of the TASC adherence-promotion intervention for adolescents with asthma in a feasibility randomized controlled trial compared to treatment as usual control arm.
Secondary Objective(s)	To assess the implementation of the TASC adherence-promotion intervention for adolescents with asthma through a process evaluation.
Research Intervention(s)/ Investigational Agent(s)	Behavioral adherence-promotion intervention delivered via technology.
IND/IDE #	Not applicable
Study Population	12-18 year olds with moderate or severe persistent asthma
Sample Size	80
Study Duration for individual participants	6 months
Study Specific Abbreviations/ Definitions	Technology Assisted Stepped Care (TASC)

2.0 Objectives

Aim 1: To test the preliminary efficacy of the TASC adherence-promotion intervention for adolescents with asthma in a feasibility randomized controlled trial compared to treatment as usual control arm. Based on preliminary development studies (ORBIT Phase I (IRB#2017-7166) and II (IRB#2018-0727)) TASC will include a stepped collection of interventions: 1) electronic educational materials, 2) utilization of an inhaler adherence monitoring device and tailored text message feedback, and 3) a telehealth problem-solving intervention.

- Hypothesis 1: The TASC adherence-promotion intervention will result in improved adherence to daily inhaled corticosteroids as measured by electronic monitoring compared to a treatment as usual control arm.
- Hypothesis 2: The TASC adherence-promotion intervention will result in improved disease severity as measured by the Composite Asthma Severity Index[75] combining symptoms, treatment, exacerbations compared to a treatment as usual control arm, and lung function as measured by mobile spirometry.

Aim 2: To assess the implementation of the TASC adherence-promotion intervention for adolescents with asthma through a process evaluation.

- Hypothesis 3: The TASC adherence-promotion intervention implementation will be successful as evidenced by high levels of reach, acceptability, usability, and sustainability.

Exploratory Aim: Examine clinical, demographic, and behavioral predictors of attendance, acceptance, and improvement in medication adherence and health within each intervention step.

Successful completion of this project is expected to have a substantial impact on public health, as the TASC intervention will result in a novel system for delivering personalized adherence-promotion intervention content to adolescents with asthma via technology to maximize reach, and as a result offer an innovative approach to improving health outcomes and decreasing health care utilization in this at-risk population.

3.0 Background

Pediatric nonadherence is a significant contributor to the public health burden of asthma. Nearly 2.4 million adolescents in the United States have asthma.[35] Although asthma can typically be controlled with daily inhaled corticosteroids, 10 Americans die each day from asthma.[36] In addition to substantial morbidity, asthma presents a significant public health burden because of the emotional impact, and annual $56 billion costs of care.[1] One major contributor to the significant public health burden of asthma is nonadherence to prescribed medical treatment.[4,37-39] Rates of nonadherence in children and adolescents with asthma range from 30-70%.[2,3,5-15,40,41] Nonadherence often leads to treatment failure, increased frequency and severity of asthma symptoms and exacerbations, variability in pulmonary function, school absenteeism, and increased expenses from medications,

additional lab tests, and health care utilization.[9,42-48] Adolescents are at particularly high risk for nonadherence[49] and morbidity, with death rates twice as high for 11-17 year olds compared to 0-10 year olds.[50-52] Although developmental factors (e.g., complacency, sense of invincibility) are barriers to adherence during adolescence,[53] adolescence is also the time when lifelong patterns of health behaviors and self-management skills are established, presenting a unique window of opportunity for intervention delivery.[31,54-56] Thus, adolescents are a critical target population to improve long-term asthma outcomes.

Behavioral interventions can improve adherence and asthma symptoms in adolescents. A recent systematic review of behavioral interventions to improve asthma management outcomes for adolescents[57] documented improvements in medication adherence,[32,34,54,58] knowledge,[59,60] quality of life,[24,32,33,58,61] proper use of mediations,[61] asthma symptoms,[16,33,58,61-63] asthma control,[16,34,64] lung function,[16,32,34] and health care utilization.[61] Promising approaches to improving adherence to daily controller medications included self-monitoring of medication use, objective monitoring of inhaled corticosteroid adherence, feedback on medication-taking behavior, increasing asthma self-management skills, goal-setting, problem-solving skills-training, and school nurse-observed therapy.[32-34,65] Broadly, these effective interventions include components consistent with the Information-Motivation-Behavioral skills model (IBM).[66] Unfortunately, the majority of these interventions require families with poor medical appointment attendance to attend at least 6 additional hours of outpatient visits and bear the burden and costs associated with traveling to the intervention.

Despite efficacious interventions, nonadherence in adolescents with asthma remains a significant public health concern due to inaccessibility and a lack of individualized tailoring. One reason for the persistence of nonadherence in adolescents with asthma is that efficacious interventions are not being disseminated or implemented in settings outside of the original study in which it is being conducted. When behavioral interventions are available, treatment session attendance is a significant barrier for adolescents and treatment content, intensity, timing, and delivery system are not personally tailored in a systematic way. Often when adherence interventions are delivered they are provided as a “one size fits all” intervention during a consultation, rather than in a self-correcting model that allows for assessment of critical outcomes at structured time points and an increase in the content, intensity, timing, and delivery of the intervention based on the patients’ needs.

Use of a technology-assisted stepped-care (TASC) intervention allows for increased access, tailoring, and dissemination of an adherence-promotion intervention for adolescents. Recent interventions have included technology to promote intervention delivery such as web-based tailored asthma education sessions,[17-22,67,68] tailored text messages,[24,25,27,69] and electronic monitoring combined with feedback.[28,30,70] A stepped-care intervention system delivered via technology allows for the delivery of the ideal care to the right patient at the right time using a delivery system (mobile phone) that is engaging for adolescents. The TASC intervention will utilize the least burdensome (both in terms of cost and personal inconvenience for the patient and the amount of time required of the interventionist) interventions while still providing significant health improvements and reserving high intensity treatment for patients who do not benefit from

simpler treatments.[39] Based on the technology-based adherence intervention literature and previously collected qualitative data (see preliminary studies (IRB #2017-7166; IRB#2018-0727)), this TASC intervention will be most effective and engaging for adolescent patients if it includes an information component, motivation component, and behavioral component.[66] Specifically, the TASC adherence-promotion intervention will include the following three steps: 1) Information: asthma management app, 2) Motivation: Inhaler adherence monitoring and feedback via text messaging, and 3) Behavior: Problem-solving and behavior skills training via telehealth. With the TASC intervention, a patient whose adherence improves as a result of utilizing the asthma management app (Step 1) will continue to receive only this strategy while an adolescent whose adherence does not improve will receive the more intensive treatment of personalized adherence feedback via text messaging).

Combining a stepped-care adherence-promotion intervention with the use of technology to deliver intervention content and obtain real-time adherence monitoring creates a system that is self-correcting. Adherence results will be systematically assessed so that treatment provision changes can be made if current treatments are not achieving significant improvement. This allows children to receive optimal treatment content, intensity, timing, and delivery while also allowing clinicians to intervene with as many patients as possible, therefore saving time and money because patients are only receiving the level of care that they need. Although medical care is often provided in a stepped-care fashion, there have been no adherence-promotion interventions to date for adolescents with asthma that are administered in a stepped-care framework. TASC will be a novel and engaging intervention that leverages adolescent use of technology to increase adherence to treatment and improve health outcomes.

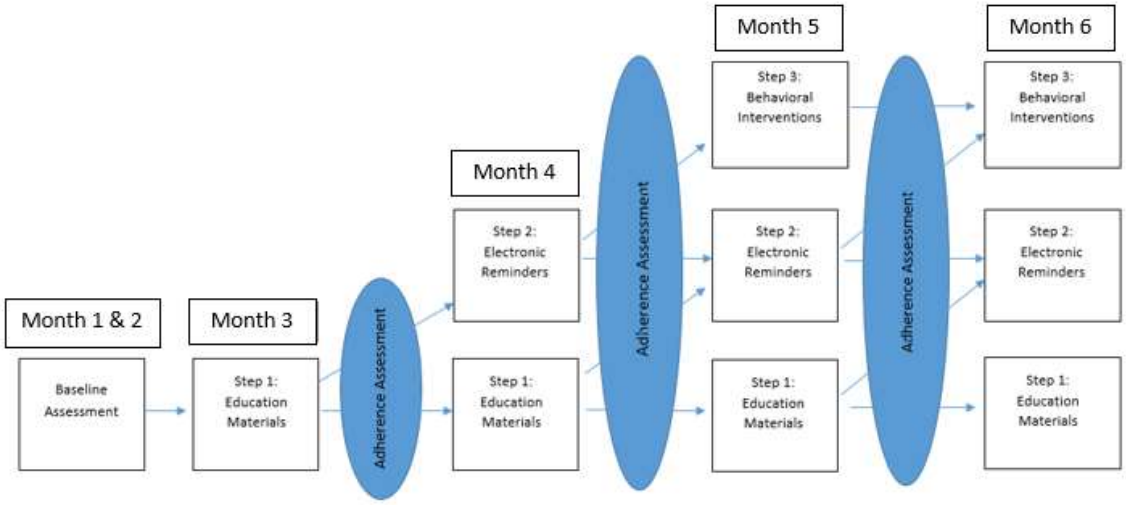
4.0 Study Endpoints

The primary study end point is post-treatment.

5.0 Study Intervention/Investigational Agent

The TASC intervention will be delivered using technology so that participants do not need any resources to travel to appointments. Step 1 (Information) will include electronic educational information via an asthma management app related to asthma symptoms and triggers, attacks, self-monitoring, treatments, action plans, and automated text message medication reminders. Step 1 will be provided to all adolescents. Adherence will be electronically monitored, but feedback will not be provided. Step 2 (Motivation) will include electronic monitoring of adherence and personally tailored feedback via text messages. Adolescents will be given access to the adherence tracking smartphone app and graphs of their inhaler adherence. Adolescents will also receive brief, personalized text messages that provide supportive motivation and directive, tangible actions. Step 3 (Behavioral) will include problem-solving telehealth intervention with a trained clinician. Four telehealth sessions individually tailored to the unique needs and barriers of the adolescent will be provided. These will be based on a functional analysis via objective adherence data, graphical feedback, and discussion of adherence patterns allowing for a comprehensive understanding of specific behavioral factors interfering with adherence.

Behavioral treatment plans will be modified based on a patient's progress in treatment and ability to achieve short-term adherence goals. Patients will also be contacted via text messaging to assess success with specific adherence plans between sessions based on objective data. This telehealth intervention will be delivered to adolescents' cell phones via video conferencing software. For each telehealth session, adolescents will also place a food order with their interventionist, which will be delivered to the participant via food delivery service (e.g., restaurant delivery, Uber Eats, GrubHub, DoorDash, etc.).



6.0 Procedures Involved

The current study involving human subjects consists of a Randomized Controlled Trial to test the feasibility, effectiveness, and implementation of the TASC intervention as compared to a treatment as usual group. A total of up to 80 adolescents with moderate or severe persistent asthma between the ages of 12-18 years will be randomized to TASC (n=35) or treatment as usual (n = 35). After adolescent participants have met inclusion criteria, completed baseline assessments, and have been enrolled in the feasibility RCT, they will be randomized to either TASC or Treatment As Usual (TAU). The statistician will make the randomization schedule and the principle investigator will maintain randomization schedule. Outcomes measures (adherence and disease severity) will be assessed at baseline, monthly during active treatment, and at post-treatment, with the primary endpoint being post-treatment.

Participants will be enrolled in the study for a duration of six months. First, participants will complete baseline questionnaires related to demographic, and clinical predictors of adherence and asthma. Participants will be randomized following completion of baseline measures. A smart phone prepared by the CCHMC IT team with a data plan will be provided to participants who do not have their own cellphone. Propeller or FindAir adherence caps will also be provided to all participants and utilized for 2 months without

feedback to obtain baseline adherence. If the participant did not bring their inhalers to the appointment, a coordinator will follow up with the patient to ensure that the Propeller or FindAir sensors are properly attached to the patients' inhalers. In addition, all participants receive a mobile spirometer (Spirobank Smart) to track their lung function throughout the study. The spirometer connects to an app (Propeller or FindAir) via Bluetooth. This app allows the participant to perform pulmonary function tests (PFTs) and view the results of these tests, such as their forced expiratory volume (FEV1) as well as other lung function parameters. Participants will be asked to use the spirometer at least once a month when completing study visits over the phone with a study team member. Following the baseline visit, a 8 week run-in phase will be completed to assess baseline adherence using electronic inhaler monitoring. After 4 weeks in baseline, the coordinator will call the participants in TASC and TAU for their first monthly phone call. After obtaining 8 weeks of baseline adherence data, the coordinator will call the participants in TASC and TAU for their second monthly phone call. The coordinator will calculate baseline adherence and obtain data for the Composite Asthma Severity Index (CASI) and the Asthma Control Test (ACT) for TASC and TAU participants. For TASC participants only, the coordinator will introduce Step 1 of the intervention for all participants. Adherence checks will continue to occur every four weeks for the duration of the study for all participants and adherence <68% will prompt movement from one level of treatment to the next for TASC participants only. The study coordinator will calculate the participant's adherence percentage prior to the monthly telephone call. During the call, the coordinator will tell the participant if they will get moved up to the next step and explain what they will be doing during that step. TASC participants may remain at a treatment level for more than four weeks and may complete 1, 2, or 3 interventions steps during the 5 month study depending on the adolescent's adherence.

Brief measures will be completed by patients online via REDCap. Participant specific data such as asthma severity, lung function, and adherence will be collected through the Propeller Health or FindAir mobile phone application, TreatSmart web portal, and via telephone. Clinical chart reviews will be conducted by study staff to provide an accurate estimate of lung function and disease severity from the date of consent to the end of study date.

Adherence Assessment:
Medical chart reviews will be conducted by study personnel to obtain information on medication regimen.

- **Electronic Monitoring:** The Propeller Health or FindAir monitoring system includes a Bluetooth enabled sensor that attaches to the patient's inhaler. This sensor records every dose, or "puff", the patient takes and sends it to a corresponding online database that is accessible to study staff. All participants will be given this sensor at baseline. Patients will not receive medication adherence feedback during the first month of the study as baseline inhaler adherence data will be collected during this time. TASC participants who move into Step 2 of the intervention will have access to their adherence via the Propeller Health or FindAir application. Study staff will have

access the patient's adherence from a daily, weekly, and monthly standpoint through the Propeller Health or FindAir provider portal.

- **Adolescent Barriers to Medication Scales (AMBS):** The AMBS is an 18-item validated measure of perceived barriers to medication adherence in adolescents. The wording will be modified slightly to match asthma treatment regimens. Good internal consistency and construct validity have been documented. The participant's AMBS score will be obtained at the baseline visit via REDCap questionnaire and again via phone at the end of the study.
- **Asthma Responsibility Questionnaire (ARQ):** A brief validated measure that assess patterns of family responsibility for asthma management and the division of family responsibility for 10 asthma management tasks. Good internal consistent and convergent validity have been documented[84]. Participants will complete the ARQ at the baseline visit via REDCap and again at the end of the study via phone.
- **COVID-19 and Learning Questionnaire:** A brief set of questions that assesses the current learning environment and its consistency to evaluate the impact on adherence. The participants' responses will be obtained verbally and recorded in an excel database. At each of the subsequent study visits, the study coordinator will check-in with participants to see if there have been any changes to their school schedule since their previous visit.

Lung Function Assessment:

- **MIR Spirobank Smart ™:** The mobile spirometer records multiple parameters of the patient's lung function including FEV1 (forced expiratory volume), PEF (peak expiratory flow), FVC (forced vital capacity), FEV1/FVC ratio, FEV6, and FEF2575 (forced expiratory flow). The spirometer sends the FEV1, PEF, FVC, FEV1/FVC, FEV6, and FEF2575 values to the corresponding mobile phone application, Propeller Health or FindAir, which is directly accessible to the patient. Other values will be accessible to study staff through a secured database. Participants will be able to view their previous lung function data as well as adherence data within the phone application. Participants will also be asked to use their spirometer while on the phone with the study coordinator during their monthly visits.

Disease Severity Assessment:

- **Composite Asthma Severity Index (CASI):** The participants' CASI score will be calculated through the TreatSmart program on a CCHMC secured laptop. The TreatSmart software web-based program, developed at CCHMC and hosted on a CCHMC secure server, will be used to determine the participant's symptom burden, health care utilization, systemic corticosteroid use, and current medication use to determine the level of asthma severity/control the participant has. The study coordinator will collect this information from the participant at baseline and then once a month during the study telephone call and will enter the data into the program. The program also makes an initial treatment recommendation based on the National Asthma Education and Prevention Program (NAEPP asthma guidelines) if the

participant's asthma meets the definition of persistent asthma and if their treatment dose should remain the same or be changed based on their level of control. This program will also produce a visit summary and asthma action plan. The CASI and Treat Smart have both been validated by ICAC.

- **Asthma Control Test (ACT).** The ACT will be used as a measure of disease severity in this study. The ACT is a 5-question scoring tool designed for patients with asthma who are 12 years and older. The questions ask the patient to rate their asthma severity, symptom frequency, control, and inhaler use on a scale of 1-5. The total score is calculated by the sum of each response, which determines how well-controlled the patient's asthma is on a scale from 5-25. The survey will be conducted at the initial visit and then via telephone (once a month throughout the study) and the ACT scores will be recorded in a password-protected database within a secured CCHMC server.

Behavioral Assessment:

- **Behavior Assessment System for Children-Third Edition, Self-report of Personality (BASC-3-SRP-A)[74]:** The BASC-3 is a widely used, reliable (α= 0.94 – 0.96 , test-retest r= 0.81 –0.82), and valid inventory to assess emotional and behavioral symptoms in adolescents and young adults (ages 13-21). Different forms are available for children and adolescents, based on age. This self-report version is completed by adolescents. The BASC questionnaire will be completed at the baseline visit and again at the end of the study via phone. Data collected from the questionnaires will be stored in a password-protected database within a secured CCHMC server.

Asthma Knowledge Assessment:

- **Knowledge Questionnaire:** A 13-item questionnaire assessing individual's knowledge of asthma symptoms, triggers, and medications. Participants rate their level of agreement to each statement on a scale from 'Strongly Agree' to 'Strongly Disagree.' This questionnaire will be completed at the baseline visit.

Hardship Assessment:

- **Hardship Questionnaire:** A 19-item validated questionnaire assessing the financial strain of individuals within a household. [80, 81, 82, 83] Participants will complete this measure at their baseline visit.

Technology Use Assessment:
The technology use measures will be completed either at baseline via REDCap or at the secondly monthly study visit via phone.

- **Autonomy and Competence in Technology Adoption Questionnaire (ACTA):** A 10-item measure of why people adopt use of a technology (i.e. download an app, register with a website, purchase a wearable device, etc.). The ACTA is based on the Self-Regulation Questionnaire scales used to measure behavior in other settings, including exercise, learning, and health care. Participants respond to self-regulation statements on a scale of 1 to 5, 1 being 'not at all true' and 5 being 'very true.' Based on the SRQ scales, the responses on the autonomous items are averaged to form the autonomous regulation score for the target behavior and the responses on the controlled items are averaged to form the controlled regulation score for the target behavior. Participants will fill out the ACTA questionnaire at their baseline visit via REDCap.
- **Technology-based Experience of Need Satisfaction- Task questionnaire (TENS-Task):** An 8-item measure of participant's competence, autonomy, and relatedness in managing their asthma using technology. Participants rate their level of agreement to each statement on a 5- point Likert scale (1= Do Not Agree, 5= Strongly Agree). Participants will complete this questionnaire at the baseline visit and again via telephone during their second monthly phone call. Responses will be entered into REDCap.
- **Technology-based Experience of Need Satisfaction- Interface questionnaire (TENS-Interface):** A 15- item measure of participant's competence, autonomy, and relatedness in using technology. Participants rate their level of agreement to each statement on a 5- point Likert scale (1= Do Not Agree, 5= Strongly Agree). Participants will complete this questionnaire via telephone during their second monthly phone call and answers will be entered into REDCap.
- **Technology Effects on Need Satisfaction in Life (TENS- Life):** The TENS-Life is a 10- item measure of the extent to which a user perceives that the use of a particular technology has had an influence on the satisfaction of basic psychological needs in their life. It is based on the validated Basic Psychological Need Satisfaction and Frustration Scale (Chen, Vansteenkiste, et al., 2015).[79] Participants rate their level of agreement to each statement on a 5- point Likert scale (1= Do Not Agree, 5= Strongly Agree). Participants will complete this questionnaire via telephone during their second monthly phone call.

Feasibility:

- **Attendance/participation rates:** Participation rates will be measured different ways for each step. The first measure will be how often participants accessed the electronic material (asthma management app, FindAir, and/or Propeller Health app), the second measure will be how many responses to directive text messaging were received, and the third measure will be attendance to the telehealth sessions.
- **Feasibility/Acceptability Questionnaire:** A 5-31 item measure of format, content, length, skills and acceptability of the intervention will be given to participants in the form of a questionnaire at the end of each step and the end of the study.

- **System Usability Scale (83):** A 10 item, Likert scale giving a global view of usability will be given to participants in the form of a questionnaire at the end of each step and the end of the study.
- **Acceptability of Intervention Measure (AIM):** A 4 item measure of participants' belief that the intervention is acceptable will be given at the end of the study.
- **Intervention Appropriateness Measure (IAM):** A 4 item measure of participants' perception that the intervention is appropriate will be given at the end of the study.
- **Feasibility of Intervention Measure (FIM):** A 4 item measure of participants' belief that the intervention is feasible will be given at the end of the study.
- **Credibility/Expectancy Questionnaire (CEQ):** A brief, 6-item validated measure of treatment credibility and outcome expectancy. The wording of the items will be modified slightly for the current intervention, but the format and response options will remain the same. Internal consistency and test-retest reliability of the CEQ range from .75- .85[85]. Participants will complete the CEQ via phone at their second visit.

Implementation:

- **Implementation:** Treatment fidelity and time needed for the intervention will be assessed. Treatment fidelity will be assessed through fidelity checklists created specifically for each intervention session. Sessions will be timed and the number of weeks to complete the session will be tracked to determine the average length of time needed for the intervention.
- **Reach:** Enrollment rate of high-risk or underserved individuals, reasons for declining participation, and representativeness of the sample will be assessed and monitored
- **Potential for Sustainability:** Process evaluation regarding the facilitators/barriers to delivering TASC intervention, possible facilitators and barriers for sustaining intervention after study completion, and feedback regarding intervention changes that could improve adoption or sustainability.
- **Perceived Characteristics of Intervention Scale (PCIS):** 19 item measure of interventionist's views toward the study intervention. This questionnaire will be completed at the end of the study.

	Baseline (in person or via phone)	Follow up (via phone)	Follow Up (via phone)	Follow Up (via phone)	Follow Up (via phone)	Follow Up (via phone)	Final Visit (via phone)
Measures	Visit 1	Visit 2 (1 month)	Visit 3 (2 months)	Visit 4 (3 months)	Visit 5 (4 months)	Visit 6 (5 months)	Visit 7 (6 months)
Electronic Monitoring	X	X	X	X	X	X	X

AMBS	X						X
ARQ	X						X
COVID Questionnaire	X	X	X	X	X	X	X
Mobile Spirometry	X	X	X	X	X	X	X
CASI	X	X	X	X	X	X	X
ACT	X	X	X	X	X	X	X
BASC-3	X						X
Knowledge Questionnaire	X						
Hardship Questionnaire	X						
ACTA	X						
TENS-Task	X			X			
TENS-Interface	X			X			
TENS- Life	X			X			
Feasibility Step 1				X			
Feasibility Step 2*					X	X	X
Feasibility Step 3*						X	X
Acceptability Questionnaire							X
SUS*				X	X	X	X
AIM							X
IAM							X
FIM							X
CEQ			X				

*Depending on when or if the participant is moved into Step 2 and Step 3 of the intervention, they will complete these questionnaires when they finish the step or they may not complete these questionnaires.

These questionnaires will be filled out by TASC participants only.

7.0 Data and Specimen Banking

Not applicable.

8.0 Sharing of Results with Subjects

The results will not be shared with the participant's primary care physicians.

9.0 Study Timelines

Participants will be enrolled in the study for a duration of 6 months. It is anticipated that all participants will be enrolled at the end of the 5th year of the study. It is anticipated that primary data analyses will be completed a year after study enrollment is complete.

10.0 Inclusion and Exclusion Criteria

Eligible adolescents will be identified through electronic medical records and recruited during outpatient medical visits or via telephone. Adolescents with a history of nonadherence per physician report will be targeted.

Inclusion Criteria:

- Patient age between 12-18 years
- Patient is diagnosed with severe-persistent or moderate-persistent asthma per NAEPP asthma guidelines
- Patient is prescribed at least one daily inhaled controller medication or a daily combination inhaled corticosteroid and long-acting beta-agonist and a beta-agonist bronchodilator
- English fluency for patient, caregiver, and clinician

Exclusion Criteria:

- Significant cognitive deficits that may interfere with comprehension per medical team or chart review
- Diagnosis of serious mental illness (e.g., schizophrenia)
- Diagnosis of pervasive developmental disorder
- Active chronic disease apart from asthma or allergic disease (e.g. Bronchiectasis, pulmonary hypertension, and moderate or severe tracheomalacia)
- Patient receives school administered daily controller medication at the time of the enrollment visit

11.0 Vulnerable Populations

This study includes vulnerable subjects (children). Our research team has extensive experience with the unique needs of this population, thus this study presents minimal risk to patients, no greater than those encountered in routine behavioral assessment and clinical care. There are no medical risks. The assessments are similar to tasks conducted in our outpatient clinics. Intervention sessions will utilize evidence-based strategies similar to those conducted clinically in outpatient clinics. It is possible that participants may feel uncomfortable responding to questions about their adherence, social support, medication knowledge, problem-solving or barriers to adherence, asthma responsibility, or behavioral difficulties. All participants will be reminded that they can decline to answer any questions if they choose without negative repercussions. The PI, Rachelle Ramsey, PhD is a licensed Clinical Psychologist and will be available to participants at any time during study participation. Consistent with HHS regulations for minimal risk studies, adolescent assent and parental consent will be obtained. Trained study staff will obtain-age appropriate written information consent/assent. All pertinent aspects of

consent/assent will be reviewed verbally and in writing including study purpose, risks/benefits, confidentiality, and right to withdraw. Patients will be informed that their care at CCHMC will not be affected whether they choose to participate in the study and that they are able to withdraw at any time. Study staff will address all questions and concerns. No assessment procedures will occur until after parent consent and adolescent consent or assent are obtained.

12.0 Local Number of Subjects

Up to 80 adolescents will be enrolled in the current study.

13.0 Recruitment Methods

Adolescents will be recruited through the CCHMC Asthma Center, which conducts 4500 patient visits each year. Eligible adolescents will be identified through electronic medical records and approached during outpatient medical visits. Adolescents with a history of nonadherence per physician report will be targeted. Study staff will meet with interested adolescents and parents to confirm eligibility and obtain written consent/assent. Adolescents may also be recruited via telephone. For the patients study staff plan to recruit via phone, a recruitment letter will be mailed or emailed to eligible families with upcoming pulmonary appointments, which will describe the study briefly and include an "opt out" phone number to call if they do not wish to be contacted about the study. Two weeks after sending the letters, study staff will call potential participants to discuss the study more thoroughly. Reasons for decline and sample composition will be tracked throughout the study to ensure accurate representation and to examine the reach of the intervention based on the enrollment rate of high-risk or underserved individuals.

Participants will be compensated for their participation in the amount of $50 for the baseline assessment, $20 at the end of month 1, $20 at the end of month 2, $25 at the end of month 3, $30 at the end of month 4, $40 at the end of month 5, $75 at the end of the study. In addition, participants will be paid $10 a week for syncing their Propeller or FindAir caps in conjunction with the Step 2 texting intervention, allowing the interventionists to obtain the data needed to complete the intervention. Participants who qualify for behavioral intervention sessions will be paid $15 per session for up to four sessions. In the event that a study phone is not returned, we will attempt via phone and email to reach the family and set up a way to retrieve it in person or via mail. Given the high cost of the phones, if, after several months it is still not returned, we may offer an incentive of $50 for the safe return of the working mobile device, no questions asked.

Families will be compensated using a reloadable debit card (ClinCard). The ClinCard will be given to families at the initial visit and compensation will be loaded once their initial visit is complete. In addition, families will receive a handout with instructions on how to use the debit card (Appendix 19.B - ClinCard Debit Card handout). Families are encouraged to keep their debit card for future visits but, should they need another card, it will be provided to them at no cost. Cards will be loaded by research coordinators immediately after a visit is completed.

14.0 Withdrawal of Subjects

Participants may withdraw from the study at any time and will be informed of this right verbally and in writing during the consent process. The principle investigator may remove participants from the study for abuse of CCHMC device privileges (see cell phone contract).

15.0 Risks to Subjects

This is a minimal risk study. All behavioral assessments and questionnaires have been used in research without any reported negative effects; rarely, participants experience mild temporary distress related to completion of behavioral measures. The adherence trackers (Propeller Health or FindAir) that will be provided to participants are registered with the FDA as a Class 1 Medical Device and therefore only pose minimal risk. Families also might be slightly inconvenienced by participating over a short period of time.

Several precautions will be taken to minimize the risk, discomforts, and inconveniences associated with this protocol. First, the PI is a licensed clinical psychologist and will oversee all study components. Thus, in the unlikely event of psychological distress resulting from questionnaires or assessment components, appropriate treatment and/or referrals can be easily made. All assessment components will be completed online or in conjunction with a pulmonary clinic appointment to lessen the burden of time and travel for families.

Knowledge gained in this study has the potential to improve treatment of pediatric asthma by enhancing disease management skills that, consequently, would improve treatment outcome in this population. The minimal risk posed to participants by this study is acceptable given that the knowledge that reasonably may be expected to result is substantial to the overall treatment of these patients and their families.

16.0 Potential Benefits to Subjects

Data from this project will inform clinical treatment of asthma through the empirical testing of an adherence-promotion intervention for adolescents with asthma. There is no guarantee of direct benefit to study participants. It is anticipated that at least some of the participants in this trial will benefit from the services provided. It is also anticipated that the pilot trial will provide important findings relative to the large-scale dissemination and implementation of the TASC intervention, ultimately benefitting additional patients with asthma.

Knowledge gained in this study has the potential to improve medication adherence in adolescents with asthma through the use of a technology-assisted empirically-supported behavioral intervention that is ready for dissemination. Despite existing adherence-promotion interventions for adolescents with asthma, nonadherence remains high and no technology-assisted interventions that can be easily disseminated are available. If this pilot trial is successful, there are pragmatic public health and clinical practice changes

that might emanate from this research. The study has the potential to advance existing adherence-promotion intervention science by shedding light on specific processes of change targeted by feedback and problem-solving based interventions. Our proposed examination of demographic factors may also help to explain why interventions work for some adolescents with asthma, but not others. The degree of risk to which study participants will be exposed in the proposed protocol is low. By contrast, the potential and probable benefits to be derived are substantial, insofar as the results will be used to enhance existing treatment or develop new interventions for this population. When considering the minimal risks entailed with participation and the extensive efforts proposed to limit/eliminate these risks, we feel that the potential benefits to the research community and future interventions far outweigh the potential minimal risks.

17.0 Data Management and Confidentiality

The primary outcome measure for Aim 1 at post-treatment is percent change in adherence to daily inhaled corticosteroids as measured by electronic monitoring devices compared to a treatment as usual control group. The secondary outcome measure is change in CASI scores. The expectation is that the TASC group will have an increased change in adherence and a decreased change on the CASI.

For Aim 2, the outcome measures are reach, acceptability, usability, and sustainability.

The exploratory outcome measures are clinical, demographic, and behavioral predictors of attendance, acceptance, and improvement in medication adherence and health within each intervention step.

Aim 1: **To test the preliminary efficacy of the TASC adherence-promotion intervention for adolescents with asthma in a feasibility randomized controlled trial compared to treatment as usual control arm.**

- Hypothesis 1 (H1): The TASC adherence-promotion intervention will result in improved adherence to daily inhaled corticosteroids as measured by electronic monitoring compared to a treatment as usual control arm.
- Hypothesis 2 (H2): The TASC adherence-promotion intervention will result in improved disease severity as measured by the Composite Asthma Severity Index combining symptoms, treatment, and exacerbations[30] compared to a treatment as usual control group.

The statistical test of choice for H1 and H2 will be an analysis of covariance (ANCOVA). Percent change in adherence is the primary clinical outcome of interest and change in CASI is the secondary outcome of interest. Seasonality will be controlled by recruitment of participants in waves and ensuring balanced enrollment across the study period. In the event that distributional assumptions are not amenable for analysis, nonparametric tests will be considered, as appropriate.

Aim 2: To assess the implementation of the TASC adherence-promotion intervention for adolescents with asthma through a process evaluation.

- Hypothesis 3 (H3): The TASC adherence-promotion intervention implementation will be successful as evidenced by high levels of acceptability, usability, reach, and sustainability.

For H3 acceptability, descriptive statistics of participant-reported and provider-reported satisfaction with intervention structure, length, convenience, and perceived impact on outcomes will be assessed[86]. For usability, the statistical test of choice will be one-sample t-test tested at the nominal $\alpha_{2\text{-tailed}} = 0.05$ level. Usability will be evaluated using the SUS and a comparison score of 71 indicating good usability.[87] For reach, representativeness of the sample and enrollment rate of underserved individuals will be assessed. For sustainability, facilitators and barriers to delivering the intervention will be assessed.

Exploratory Aim: Examine clinical, demographic, and behavioral predictors of attendance, acceptance, and improvement in medication adherence and health within each intervention step.

Mediation and moderation of treatment effects will be examined using strategies outlined by Barron and Kenny[88], Holmbeck and colleagues[89,90] using candidate covariates believed to be in the causal chain, including but not limited to, demographic characteristics, asthma symptoms, clinical presentation, treatment outcome expectancy (CEQ), and externalizing and internalizing problems (BASC).

A total of 60 participants will be needed for Hypothesis 1 analyses. Monte Carlo simulations in Mplus (version 8.1) were conducted to estimate statistical power assuming: 1) baseline adherence, asthma exacerbations, and race/ethnicity could explain between (R^2 = 0.20-0.40) 20%-40% of response variable noise variance, 2) participant attrition could range between 0%-20%, 3) alpha = .05, and 4) pre-post correlations similar to those reported in both the intervention literature and observed in our lab. The power analysis question involved identifying the smallest *d* effect size difference under these assumptions. Assuming proper handling of missing data, results showed power will be $\geq$ 0.80 for $d \geq 0.72$. Effect sizes larger than the one proposed have been documented in published studies[12,91], however, if statistical significance is not achieved, effect size estimates would inform design and power considerations for subsequent efficacy studies to further evaluate the TASC intervention. Up to 80 participants will be recruited to account for attrition.

Many procedures are in place to guard against missing or unusable data; however, missing data are almost inevitable in clinical research. The strategy for accommodating missing values is to first investigate and identify patterns of missingness, by group and variable, by using established pattern identification techniques. To the extent possible, potential mechanisms of missingness will be identified, including values deemed to be missing at random, completely at random, or not random at all. If substantial missing data are observed, parameter estimation using multiple imputation methods will be computed to estimate the missing values, and relevant predictors related to missingness will be added to our models. Sensitivity analyses will be conducted, with and without outliers/extreme values, and with and without imputed values to test the stability of our models under alternative conditions.

All data will be de-identified with the use of unique assigned study identifier codes. All electronic data will be stored on a CCHMC network server with built-in security. Treatsmart program data and web-based databases are located on a CCHMC secure server. Propeller Health or FindAir adherence data is located on their HIPAA-compliant servers and will be transferred securely to the CCHMC investigators at the end of the study for data analysis. Smartphones provided by CCHMC for use by the participants in the clinical study will be loaded with a security software program, Air Watch. Air Watch is a mobile device management technology that enables IT to deploy, configure, manage, support, and secure mobile devices from afar to provide remote configuration, trouble-shooting, and lock and wipe security. Air Watch will not be loaded on participants' personal cell phones.

Propeller Health, FindAir, Treatsmart, asthma management app, and REDCap data will be stored on a secure, HIPAA compliant server and only approved study personnel will have access to the server (MAP) and data contained within the server. Informed consent/assent documents, and W-9 tax forms will be stored on a secure network drive with limited access. Any de-identified data will be confidentially protected with the use of unique assigned study identifier codes, and a master key linking identifying patient information (e.g., MR#) with the study ID code will be secured in a different locked file. The key, used for data entry purposes, will be destroyed as soon as possible after the completion of the study. Data will be retained until final data analyses are completed; all de-identified data will then be destroyed (e.g., shredded). Weekly audits to confirm access to database repositories and web application server environments will be conducted to ensure that it is limited to the appropriate user group. In addition, private conference rooms are available at CCHMC to ensure confidentiality during telehealth visits

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

This study involves minimal risk to participants. Study personnel at CCHMC will monitor data collection, progress through treatment, any technical difficulties that may arise, adverse events, and completion of study procedures. Any adverse events (i.e., breach of confidentiality or events that are unexpected and related to the intervention) will be reported to the IRB within 48 hours. Participation will be discontinued at parent or patient request or if the investigators deem that it is in the best interest of the patient's health. The study team will provide referrals as appropriate for treatment needs resulting from any adverse events. The IRB requires yearly renewal of study protocols, which provides additional monitoring of participant safety. All other adverse events that happen in the course of the study procedures as well as minor deviations from protocol will be reported in table form at the next yearly continuing IRB review. The PI will review study data with her primary mentor at weekly meetings to ensure safety compliance and proper reporting to the IRB. In addition, the PI will have quarterly meetings with her mentorship team to monitor the progress of the study, the integrity of the treatment, discuss the need for any protocol refinements, and conduct regular safety monitoring checks of adverse

events. The PI will report any significant study related or unanticipated adverse events to not only the IRB, but also to the study sponsor based upon institutional and sponsor guidelines. Given that this pilot study is using evidence-based intervention, we believe that monitoring at the level of the PI, her mentors and research team, with oversight from the IRB and study sponsor is sufficient.

19.0 Provisions to Protect the Privacy Interests of Subjects

All research staff will participate in data safety and monitoring by reporting any emotional distress reactions or adverse events to the study PI. Participation in the study will be discontinued at parent or patient request, or if the parent or patient experiences a significant adverse event. The PI will immediately report any adverse events to the IRB. In the unlikely event of a participant necessitating medical or psychological treatment due to adverse effects of participating in a study, a member of the investigative team will make appropriate referrals and/or hospitalization within the appropriate study site.

It is possible that situations will arise in which research staff will be provided information by participants which they are legally and ethically obligated to disclose (e.g. suicidal or homicidal intent, sexual/physical abuse). In these instances, the appropriate report and/or referral for psychological intervention will be arranged and the PI, Rachelle Ramsey, PhD, will be immediately notified. All exceptions to confidentiality will be clearly outlined to the participant during informed consent.

20.0 Compensation for Research-Related Injury

Not applicable.

21.0 Economic Burden to Subjects

There is no cost for participating in the study, only time and minimal cell phone use. Study procedures will be completed online or in conjunction with pulmonary clinic appointments to lessen the burden of travel. All study components (i.e. cellular phone and data plan, inhaler attachment, and mobile spirometer) will be supplied to participants at no cost if they do not have the necessary cellular device. Families will continue to be responsible for usual costs associated with their medical care.

22.0 Consent Process

Potential participants will be consented by telephone or in person. For telephone recruitment, the consent form will be sent to families for review and a phone call will be utilized for study staff to thoroughly review the form with the family. This will allow caregivers and patients ample time to review the document and get answers to any questions. Once all questions are answered, patients and caregivers will sign the consent/assent form. Assent and parental permission will be obtained from at least one

legal guardian for individuals under the age of 18 years old. Forms can be returned to study staff by mail, email, or fax, or can be signed electronically using REDCap or SignNow, a cloud-based electronic signature platform that allows companies and individuals to sign documents from their computer, iPhone, iPad, or Android device. Each page of the consent form will be uploaded into REDcap so that the patient and caregiver can view the form. There are spaces in the REDCap form for the research participant to indicate their date of birth, whether or not they consent to the study, as well an area to type their name, sign, and date. If the research participant is under 18, there is also a space in REDCap for the caregiver or legally authorized representative to sign and date, as well an area for the legally authorized representative to provide a description of their authority. Study staff will sign and date accordingly on the signature page or in a designated space in the REDCap form corresponding to the date the forms were received, not necessarily reviewed with the family. The method used to obtain participant consent will also be written on the Informed Consent Process Note. Reasons for decline and sample composition will be tracked throughout the study to ensure accurate representation.

Participants may also be consented in person at their appointment in the Pulmonary Clinic. Study staff will thoroughly review the form with the family and caregivers and patients will be given ample time to review the document and get answers to any questions. Once all questions are answered, patients and caregivers will sign the consent/assent form. Forms can also be signed electronically via REDCap or the SignNow platform in person, using either the coordinator's CCHMC laptop or the participant's smartphone.

23.0 Process to Document Consent in Writing

In compliance with CCHMC SOP Number 41-1.6, study staff will sign and date accordingly on the signature page of each form or in a designated spaced in REDCap corresponding to the date the forms were received, not necessarily reviewed with the family. The method used to obtain participant consent will also be written on the Informed Consent Process Note. Signed consents will not be sent to Health Information Management due to the minimal risk nature of the study.

24.0 Setting

Research will be conducted at Cincinnati Children's Hospital Medical Center and satellite locations, including Green Township and Liberty Campus. Potential participants will be identified through electronic medical records and approached during outpatient medical visits or via phone following a two- week "opt out" period. Research procedures will be performed at Cincinnati Children's main campus, the satellite locations listed above for the baseline visits, or via phone.

25.0 Resources Available

Adolescents will be recruited through the CCHMC Asthma Center, which conducts 4500 patient visits each year. We will start by contacting patients in the Asthma Center, but will recruit from other clinics within pulmonary and allergy if necessary.

26.0 Multi-Site Research

Not applicable.

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28.0 Appendix

Data Safety And Monitoring Plan

The purpose of this K23 is to test the preliminary efficacy of a technology-assisted stepped-care (TASC) adherence-promotion intervention for 12-18 year old adolescents with asthma in a pilot RCT. Following a two month baseline period, adherence will be assessed monthly and adolescents will be provided with the appropriate intervention step based on their adherence to daily inhaled corticosteroids. Preliminary efficacy will be demonstrated by improved adherence to daily inhaled corticosteroids as measured by electronic monitoring devices compared to a treatment as usual (TAU) control group. Secondary outcomes include disease severity as measured by the Composite Asthma Severity Index combining symptoms, treatment, and exacerbations compared to TAU and an assessment of TASC implementation through a process evaluation assessing reach, usability, and sustainability.

This study involves no more than minimal risk to participants. The PI, her mentoring team, and study personnel at CCHMC will monitor recruitment, retention, data collection, progress through treatment, any technical difficulties that may arise, adverse events, and completion of study procedures. Any adverse events will be reported to the IRB within 48 hours. Participation will be discontinued at parent or patient request or if the investigators deem that it is in the best interest of the patient's health. The study team will provide referrals as appropriate for treatment needs resulting from any adverse events. The IRB requires yearly renewal of study protocols, which provides additional monitoring of participant safety. All other adverse events that happen in the course of the study procedures as well as minor deviations from protocol will be reported in table form at the next yearly continuing IRB review. The PI will review study data with her primary mentor at weekly meetings to ensure safety compliance and proper reporting to the IRB. In addition, the PI will have quarterly meetings with her mentorship team to monitor the progress of the study, the integrity of the treatment, discuss the need for any protocol refinements, and conduct regular safety monitoring checks of adverse events. The PI will report any significant study related or unanticipated adverse events to not only the IRB,

but also to the study sponsor based upon institutional and sponsor guidelines. Given that this pilot study is using evidence-based intervention, we believe that monitoring at the level of the PI, her mentors and research team, with oversight from the IRB and study sponsor is sufficient.

All data will be de-identified with the use of unique assigned study identifier codes. All electronic data will be stored on a CCHMC network server with built-in security. Treatsmart program data and web-based databases are located on a CCHMC secure server. Propeller Health or FindAir adherence data is located on their HIPAA-compliant servers and will be transferred securely to the CCHMC investigators for data analysis. CCHMC smartphones used by the participants in the clinical study will be loaded with a security software program, Air Watch. Air Watch is a mobile device management technology that enables IT to deploy, configure, manage, support, and secure mobile devices from afar to provide remote configuration, trouble-shooting, and lock and wipe security.

Computer files will only contain study identifier codes and will be password protected. Paper records will be stored in locked file cabinets accessible only to the PI and authorized study team members. Access to all data and subject identities will be limited to the research team. Informed consent documents will be stored in a locked location separate from study data. Medical chart data will be collected under the supervision of the PI. Summaries of these data will remain secure under the supervision of the PI and study coordinator. Private conference rooms are available at CCHMC to ensure confidentiality during telehealth visits. These risk protection methods have been used effectively by Dr. Ramsey and her mentors in previous studies.

Procedures for monitoring study safety, minimizing research-associated risk, and protecting the confidentiality of participant data

Adolescents and parents will be approached during outpatient medical visits or via telephone. Study staff will meet, in person or over the phone, with interested adolescents and parent(s) to confirm eligibility and obtain written consent/assent. The coordinator will explain the purpose of the study, what participation entails, risks and benefits of participation, data to be collected, confidentiality, privacy, procedure for discontinuation of participation, reimbursement, and contact information for study personnel. For consent obtained over the phone, the consent will be provided electronically to the patient and family ahead of time in offer to allow for time to review. Participants and parents will be explicitly told that their child's medical care will not be affected whether they choose to participate in the study or decline participation. Once any questions from the parent or adolescent have been answered, parents will sign the consent from and adolescents will sign the assent form on the same parent consent documents, which includes HIPAA authorization. A copy of the signed combined consent/assent form will be provided to the parent. Names and phone numbers of the PI and the Institutional Review Board will be provided on these consent forms. Participants and parents will also be told that they may decline to answer any questions that make them feel uncomfortable and will be reminded

of this prior to measure completion. Participants may also withdraw from the study at any time and will be informed of this right verbally and in writing during the consent process.

In the unlikely event that the content of the questionnaires causes emotional or psychological distress, the Principal Investigator, Rachelle Ramsey, PhD, a licensed Clinical Psychologist at CCHMC, or a qualified designee will be contacted immediately to assess the patient and provide appropriate referrals and/or treatment. If the matter is assessed as urgent, the PI or a qualified designate will recommend that child seek emergency medical care (e.g., go to the nearest emergency room). In situations that are not urgent, the PI or a qualified designate will provide the individual with referral information for obtaining psychological services.

We will attempt to alleviate all issues of confidentiality breaches. Confidentiality will be protected by assigning a numerical code to each research participant for data collection. Study identifier codes will be used in the web interface for data entry and adherence electronic monitor data download. No other identifying data such as date of birth, address, phone numbers, social security number, or zip code will be entered in the web interface. All exported data files will only identify participants via study identifier codes. All data will be kept in password protected electronic files on the CCHMC hard drives. All passwords will only be known to study staff directly involved in the administration and oversight of the data collection. All information collected as part of this study will be accessible only to study staff, who will complete CCHMC human subjects training to ensure familiarity with rights of research participants and protection of confidentiality. Electronic data stored on CCHMC's network is backed up nightly. The server is maintained and all backups are conducted by the Division of Information Services. Access to data and subject identities will be limited to study team members.

Informed consent/assent documents will be maintained in a locked location at CCHMC. Consents will be kept separate from participant's data. Only the study investigative team will have access to these materials. Medical chart data will be collected by trained study staff under the supervision of the PI. These risk protection methods have been effectively used by the PI and her mentors for numerous studies.

It is possible that situations will arise in which research staff will be provided information by participants which they are legally and ethically obligated to disclose (e.g. suicidal or homicidal intent, sexual/physical abuse). In these instances, the appropriate report and/or referral for psychological intervention will be arranged and the PI, Rachelle Ramsey, PhD, will be immediately notified. All exceptions to confidentiality will be clearly outlined to the participant during informed consent.

We will be using technology for the intervention; thus, it is possible that privacy can be lost when using the internet, cell phones, computers, or tablets. Parents/legal guardians will be advised about this potential loss of privacy. For study purposes, we will continue to code everything to a participant number or use language that minimizes identification of a particular participant by name or HIPAA-based information.

Security for web-based applications is provided through a Secured Socket Layer certificate allowing for 128-bit encryption between client and server transactions as well as the secured demilitarized zone (DZD) network. Participant responses will be stored on the secured SQL server database. All data will be stored and accessed in accordance with the HCFA's Internet Security Policy and HIPAA.

Data will be stored in the secured data repository on CCHMC's internal network drive and automatically backed up and managed by the administrator. The guidelines from the Society of Clinical Data Management will be followed for security at various steps of development. Weekly audits to confirm access to database repositories and web application server environments will be conducted to ensure that it is limited to the appropriate user group

Finally, because this research study involves payment for participation, we are required by Internal Revenue Service (IRS) rules to collect and use their social security number (SSN) or taxpayer identification number (TIN) in order to track the amount of money that we pay them. Unless they have given specific permission for another use of their SSN or TIN related to this research study, we will only use their SSN or TIN to keep track of how much money we pay them, and their SSN or TIN will not be used as part of this research study.

Additional Protections for Vulnerable Subjects, Children

Consistent with HHS regulations for minimal risk studies, adolescent assent and parental consent will be obtained. Further, the minimal risk posed by this project to participants is reasonable given the resulting novel adherence-promotion intervention.

In the unlikely event that the content of the interviews, questionnaires, or intervention causes emotional or psychological distress, the PI, Rachelle Ramsey PhD, a licensed clinical Psychologist at CCHMC or a qualified designee will be contacted immediately to assess the situation and provide appropriate referrals and/or treatment.

Adolescence is a unique development period marked by significant changes in academic and occupational roles, social relationships, responsibilities and independence. Accurate assessment of the efficacy of TASC and identification of predictors of adherence relevant to this age group requires the inclusion of children ages 12-18 years. Our team's specialized training and expertise in adolescents will allow us to be sensitive to the unique needs of our study participants. We will listen carefully to any information and concerns reported by both adolescent participants and their parent/caregiver.

Procedures for handling endorsement of intent to self-harm

A question related to intent to self-harm is included in the current protocol on the Behavior Assessment Scale for Children Form. QUESTION 124 says "My life isn't worth living." If the adolescent responds with 'often' or 'always' to QUESTION 124, the PI, Rachelle Ramsey PhD, a licensed clinical psychologist with training in suicide risk and assessment or a qualified designee, will be contacted to assess the situation, including

an assessment of risk. If it is determined that there is no immediate risk or concern, the parent/legal guardian will be provided with information regarding what to do if the risk status changes at home, how to keep the child safe (e.g., removal of weapons or material that can be used for self-harm), as well as procedures to go to the local Emergency Room if risk is elevated. The adolescent will also be provided with the National Suicide Prevention Lifeline (1-800-273-TALK) hotline. If the adolescent is at risk for self-harm and has intent and means, the adolescent and their parent will be directed to go to the an emergency room for further assessment (e.g., need for a 72 hour hold, inpatient psychiatry). Regardless of the level of concern, such risks will be documented as they occur and the IRB will be notified during the continuing review. These are considered adverse events because they are expected in this population as approximately 45% of youth with asthma report depression symptoms and the suicide attempt rate has been shown to be twice the national population rates.[92] These procedures have been successfully used in prior behavioral adherence trials conducted by the PI and her mentors.

These procedures will also be followed should concerns arise regarding abuse or neglect. If, during the course of the study, research staff become aware of mistreatment of neglect of a child under the age of 18 by a parent/legal guardian, his/her partner, a relative or someone living in the home, a caretaker (e.g., babysitter, day care worker), or any person responsible for the child's welfare, we are mandated by law to contact the appropriate person or agency. If this occurs, the PI or a designee will be contacted. If abuse/neglect is suspected, a report will be initiated immediately to child protective services based on the local reporting requirements. This would be considered a serious adverse event. Such an event would be reported by the PI to NHLBI and the IRB immediately and during continuing review. Patients and caregivers will be made aware that any information obtained during their participation that suggests the potential for harm to self or others will be immediately disclosed to the appropriate individual in order to protect the patient.

Study safety monitoring schedule

The PI and mentoring team will randomly review 10% of all participant research files on an annual basis for: compliance with IRB requirements (including proper completion of all consent documents), compliance with informed consent requirements, data quality and integrity, and research assistant compliance with the study protocol.

The research team will monitor for safety and adverse events at each study visit. In the context of this study, adverse events are defined as "any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research" (http://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html). Given this definition, adverse events such as suicidal ideation and hospitalizations and emergency room visits due to asthma would be expected in this patient population but it would be very unlikely for an adverse event such as this to occur as a result of study participation. We will record suicidal ideation, hospitalizations and

emergency room visits and report these as regular adverse events during the yearly continuing review.

A serious adverse event is defined as any event that could be considered life-threatening, requires an emergency room visit or hospitalization, or may jeopardize the child's health (http://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html). All serious adverse events (such as reports of abuse/neglect) will be reported immediately (in less than 48 hours) to NHLBI and to the IRB. Such reports will include the date on which the event occurred, a detailed description of the event, a detailed accounting of the response to the event, whether the event was related or unrelated to the study, and a log of which monitoring entities were contacted.