A prospective, randomized, controlled study to assess medication adherence in children with asthma managed on BreatheSmart and feedback.

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PRINCIPAL INVESTIGATOR: Jessica Hollenbach
DEPARTMENT: The Asthma Center
INSTITUTION: CT Children's Medical Center
PHONE: (860) 837-5333
EMAIL: jhollenbach@connecticutchildrens.org

CO-INVESTIGATOR: Tregony Simoneau
DEPARTMENT: Pediatric Pulmonary
INSTITUTION: CT Children's Medical Center
PHONE: (860) 545-9440
EMAIL: tsimoneau@connecticutchildrens.org

CO-INVESTIGATOR: Craig Schramm
DEPARTMENT: Pediatric Pulmonary
INSTITUTION: CT Children's Medical Center
PHONE:
EMAIL: cschram@connecticutchildrens.org

CO-INVESTIGATOR: Craig Lapin, M.D.
DEPARTMENT: Pediatric Pulmonology
INSTITUTION: CT Children's Medical Center
PHONE:
EMAIL: clapin@connecticutchildrens.org

CO-INVESTIGATOR: Anne McLaughlin, M.D.
DEPARTMENT: Pediatric Pulmonology
INSTITUTION: CT Children's Medical Center
PHONE:
EMAIL: amclaughlin@connecticutchildrens.org

CO-INVESTIGATOR: Umit Emre, M.D.
DEPARTMENT: Pediatric Pulmonary
INSTITUTION: CT Children's Medical Center
PHONE:
EMAIL: uemre@connecticutchildrens.org

CO-INVESTIGATOR: Melanie Collins, M.D.
DEPARTMENT: Pediatric Pulmonology
INSTITUTION: CT Children's Medical Center
PHONE:
EMAIL: mcollin@connecticutchildrens.org

Co-Investigator: Natalie Shilo
Department: pediatric Pulmonology
Institution: CT Children's Medical center
Phone: 860-545-9440
Email: nshilo@connecticutchildrens.org

DOES THIS PROJECT INVOLVE ANY NICU RESOURCES? **_X_ NO ___ YES**
(patients/families, clinical/non-clinical staff, medical records)

IF YES, HAS IT BEEN REVIEWED BY DR. MOORE OR HIS DESIGNEE? ___ NO ___ YES

IF YES, SPECIFY REVIEWER: _____

IS THIS A STUDENT OR TRAINEE PROJECT? **_X_ NO ___ YES**

IF YES, INDICATE LEVEL:	**___ Medical/Dental Student** **___ Resident** **___ Fellow** **___ Undergraduate** **___ Other (specify _____)**

IF YES, HAS FACULTY ADVISOR REVIEWED THE PROTOCOL? ___ NO ___ YES

Note: Student researchers are required to attend the Scientific Review Committee meeting when their protocol is discussed.

TITLE: A prospective, randomized, controlled study to assess medication adherence in children with asthma managed on BreatheSmart and feedback.

SPONSOR

CCMC

PROTOCOL NUMBER: V.5

Contents

ABBREVIATIONS

EMD	Electronic Monitoring Devices
ICS	Inhaled Corticosteroids
BTE	Bluetooth Low Energy sensor
MA	Mobile application
ACT	Asthma Control Test
mHealth	Mobile Health
pMDI	Pressurized metered dose inhaler
ED	Emergency Department
PFT	Pulmonary Function Test
eCRF	Electronic case report forms
EDC	Electronic data capture
FEV	Forced expiratory volume
FeNO	Fractional exhaled nitric oxide

1. INTRODUCTION/BACKGROUND

Asthma affects more than 235 million people worldwide, including approximately 8.6% of U.S children (6.3 million children).[1,2] Asthma treatment is a substantial burden to the healthcare system and is responsible for more than 10 million medical office visits (close to 6% of all US medical office visits) and 1.8 million ED visits each year.[3] Regular use of controller medication is essential to prevent symptoms and relieve asthma exacerbations and thus decrease healthcare utilization and expenditure.[4]

Non-adherence to asthma medication is a common problem in patients with asthma, and young people are known to have particularly low medication adherence.[5,6] Non-adherence leads to overuse of reliever medication and more frequent severe asthma exacerbations including ED visits and hospital admissions.[4,7] Self-report consistently overestimates medication adherence making accurate assessment and intervention difficult for clinicians.[5] However, two recent reviews found mean controller adherence ranging from 20% to 34% and 38% to 71% as measured by medication possession ratio (MPR) and electronic monitoring respectively.[8,9] Thus, even the commonly cited statistic of 50% average medication adherence may underestimate the true scope of the problem.[10-12] Non-adherence is multifactorial, with contributing factors including lack of patient knowledge about asthma, poor understanding of the benefits of medication, forgetfulness, and negative attitude toward asthma.[9]

Telemanagement of chronic diseases is increasingly being employed to improve medication adherence and health outcomes, and has been shown to be cost-effective.[13] A recently developed process model for optimal asthma care demonstrates the need for improved understanding of patient medication use behavior and how adherence interventions can impact clinical outcomes.[14] A number of studies have improved medication adherence through incorporation of electronic reminders such as text messages across the spectrum of chronic diseases.[15] Recently a number of studies have looked specifically at the use of such messages along with medication-use tracking in asthma have been able to show mean improvement in adherence from 10-52 percentage points.[16-23] While promising, these interventions have focused on the use of audiovisual reminder systems[16, 21-23] that rely on having access to the inhaler itself or are simply based on SMS messages.[17,18] Such interventions are limited in their ability to engage participants for improved disease self-management and self-monitoring compared to more comprehensive approaches, known to be key for sustained asthma telemanagement and mHealth approaches.[13]

Importantly, mobile applications allow for better sustained patient engagement and have been successfully implemented in other disease spaces to improve medication adherence and outcomes.[13] Mobile applications offer the opportunity to be scaled to the U.S. population-at-large and can be sustained due to the front-end cost of development and low staff resources required for maintenance once the product is built. Additionally, the ability to relay adherence data directly to clinicians either via a patient portal or into the EMR provides opportunity to direct care coordination efforts and resources towards those participants who are most in need, and provides information that can be used for point-of-care treatment decision making.

2. STUDY TITLE

A prospective, randomized, controlled study to assess medication adherence in children with asthma managed on BreatheSmart and feedback.

3. JUSTIFICATION

Non-adherence to controller medication is a common problem in children with Asthma, resulting in overuse of reliever medication, increased asthma symptoms, more frequent Asthma attacks, and increased emergency room visits and hospital admissions.4 Additionally, current absence of a gold standard to measure adherence forces clinicians and researchers to rely on patient-self report, which is notoriously inaccurate, to support clinical decision making. Many young patients suffer from both intentional and non-intentional non-adherence, thus an appropriate intervention must address both types. Current studies using electronic monitoring devices (EMDs) primarily focus on non-intentional non-adherence through reminder systems and thus are limited in their ability to engage patients for long-term behavior change.

This trial addresses an important knowledge gap by evaluating whether EMDs with a combination of reminder system and patient education can prove to be effective in increasing adherence rates and can be used in clinical practice to achieve better asthma control and outcomes through improved patient and clinician engagement.

4. OBJECTIVES

The objectives of this study are to determine if the addition of the BreatheSmart platform improves medication adherence and health outcomes in children with persistent asthma who are managed with inhaled corticosteroids.

5. BREATHESMART

5.1. BreatheSmart

A mobile application designed for use with iOS and Android operating systems. Using Bluetooth to connect, this mobile application syncs with HeroTracker to facilitate the collection of medication adherence data.

5.2. HeroTracker

A wireless Bluetooth-enabled inhaler sensor that tracks medication dosage and adherence. Designed for both controller and rescue medications in diskus and MDI formats.

5.3. CoheroConnect

A HIPAA compliant cloud-based application allowing data to be aggregated and readily available as actionable information for clinicians and caregivers managing children on BreatheSmart.

6. STUDY DESIGN

This is a prospective, randomized, controlled study of children with persistent asthma who are managed on daily inhaled corticosteroids (ICS). 75 children will be randomized **2:1** into one of two arms:

- 50 children will be randomized to BreatheSmart, comprised of:
    - BreatheSmart mobile application that tracks medication usage and sends real time reminders
    - HeroTracker sensor that counts dosage and monitors real-time medication adherence
    - CoheroConnect provider portal that allows the Investigator to monitor real-time adherence and to provide targeted outreach to children with low adherence (intervention arm)
- 25 children will be randomized to “standard of care” (control arm). These patients are reminded to adhere to the prescribed standard of care therapy provided by their clinician during their clinical encounters and when the family calls to report an illness.

6.1. Endpoints

6.1.1 Primary:

The study's primary objective is to estimate the relative improvement in medication adherence among children using BreatheSmart with feedback compared to control at 6 months.

6.1.2 Secondary:

Important secondary objectives include the extent to which BreatheSmart system improves the following when compared to control from baseline to 6-months:

- asthma control as measured by the Childhood Asthma Control Test (ACT)
- lung function as measured by FEV1 and FEV1/FVC ratio compared to standard of care
- the correlation between changes in medication adherence and changes in FEV1 and FEV1/FVC ratio.
- the overall number of provider visits for asthma related adverse events (number of exacerbations leading to acute Provider intervention, ER visits, hospitalizations, or requiring oral systemic corticosteroid therapy)
- number of missed school days

7. STUDY POPULATION

This study will enroll children who have been diagnosed with persistent asthma for at least 6 months' duration and who are showing evidence of poorly controlled disease. 75 children will be recruited from CT Children's Medical Center Pulmonary Clinic and East and West Primary Care.

7.1. Inclusion and Exclusion Criteria

Inclusion and Exclusion Criteria

Inclusion criteria:

- Age 8 to 17
- Diagnosis of persistent asthma
- Prescribed an inhaled corticosteroid (ICS) for at least one month prior to enrollment
- Use of a pressurized metered dose inhaler (pMDI) compatible with the Cohero mHealth Herotracker (See Appendix)
- Parent/child possess a compatible smartphone (iOS 8.0 or higher)
- English or Spanish speaking

Exclusion criteria:

- Presence of another chronic lung disease or condition such as cystic fibrosis, interstitial lung disease, chronic lung disease of prematurity, recurrent aspiration, or presence of tracheostomy
- Presence of other chronic medical condition such as congenital heart disease or immunodeficiency
- Presence of other comorbidities that, in the opinion of the investigator, will interfere with collection of study procedures, or limits life expectancy to < 1 year
- Currently pregnant or planning to become pregnant during the trial period

7.2. Sample Size Estimates

There is no pilot data available to inform a sample size analysis. In addition, our sample size is limited by our supply of HeroTracker devices (50). As this is an exploratory study, we hope our findings will inform future sample size analyses for studies of similar focus with a larger cohort.

7.3. Recruitment

Due to the shortage of space and high patient volume at the CCMC pulmonary office, based on the scheduled patients for the day, research personnel will identify potentially eligible patients based on information will be gathered from the "Pulmonary Snapshot" feature in EPIC. These data include patient age, asthma diagnosis and prescribed medicines. Research personnel will also be identifying potentially eligible patients at the East and West Primary care through the "Primary Care Sanpshot" features in EPIC. Potential participants will only be approached if he/she meets the following inclusion criteria: age between 8-17 years, documented diagnosis of persistent asthma and/or prescription of an inhaled corticosteroid. Once this is confirmed, the research personnel will approach the patient to administer the screening questionnaire to confirm that the child meets all the inclusion and exclusion criteria. Children could also be referred to this study by their healthcare provider if he/she feels that the patient qualifies for entry into the study based upon the Inclusion/Exclusion Criteria. If eligible, the parent will be asked to participate in the study and presented with the informed consent document which will include the parent's consent to utilize the relevant screening and baseline data for the purposes of this study.

7.4. Informed Consent

The primary investigator (or designee) will discuss the study in detail with the child and parent and describe the potential risks and benefits. If the parent agrees for their child to participate, a legally effective informed consent will be obtained. The consent process will be documented in the study chart and the parent will receive a copy of the fully executed informed consent form for their records. All children participating in this study will complete assent.

7.5. Participant Numbering

To maintain confidentiality, the participant's name will not be recorded on any study documents other than the informed consent form. All participants that provide informed consent will be assigned a unique alphanumeric code that will identify them throughout the course of the study.

8. STUDY PROCEDURES

All participants will be seen at screening/baseline, 90 and 180 days' post randomization where the following assessments will be performed.

8.1.Screening Assessments

The study staff will interview the parent and child and document the following:

- Type of mobile device and version number of the operating system in use
- Email address
- Age/gender/ethnicity
- Parent Income level/education level/medical insurance type
- Date of asthma diagnosis
- Other comorbidities
- Use of inhaled corticosteroids and other inhaled therapies for asthma
- Use and timing of oral systemic corticosteroids
- Use of other concomitant medications
- Medication refill information (obtained through pharmacy records)
- ACT

8.2.Randomization

If the child is eligible and they wish to participate they will be randomized in a 2:1 allocation to BreatheSmart **or** to standard of care. As we have a limited supply of HeroTracker devices and the CoHero platform does not provide a feasible way to execute any degree of blinding, this will be conducted as an open trial where both groups (control and intervention groups) will be treated as equally as possible. Randomization will be stratified by age at the time of enrollment (8-13 years, 14-17 years) and blocked in randomly permuted sequences of 4.

8.3.Baseline Assessments

8.3.1. Control Participants

Control participants will be reminded to adhere to the standard of care therapy, as prescribed. The following assessments will be recorded:

- Concomitant medications

- Measurement of lung function including FEV1, FEV1/FVC ratio, FeNO (standard clinic measurement only assessed in the Pulmonary clinics)
- Child Asthma control test (ACT) questionnaire
- Exacerbation of asthma episodes (obtained through self-report and chart review) requiring:
  - ○ Courses of oral steroids
  - ○ Doctor visits outside of standard of care
  - ○ ER visits
  - ○ Hospitalizations
- Missed school days
- PedsQL asthma module (patient and parent report)
- Test of Adherence to Inhalers
- Pharmacy refill data for asthma prescriptions during the previous 6 months

8.3.2. Active Participants

Active participants will be reminded to adhere to the standard of care therapy, as prescribed. They will be trained to and provided with the BreatheSmart application and Herotrackers. The following assessments will be recorded:

- Concomitant medications
- Measurement of lung function including FEV1, FEV1/FVC ratio, FEF25-75, FeNO (standard clinic measurement, completed by participants recruited for the pulmonary clinic)
- Child Asthma control test (ACT) questionnaire
- Exacerbation of asthma episodes (obtained through self-report and chart review) requiring:
  - ○ Courses of oral steroids
  - ○ Doctor visits outside of standard of care
  - ○ ER visits
  - ○ Hospitalizations
- Missed school days
- PedsQL asthma module (patient and parent report)
- Test of Adherence to Inhalers
- Pharmacy refill data for asthma prescriptions during the previous 6 months

8.4. Follow-up

All participants in both groups will be seen at 90 and 180 days' post randomization (+/-20 days correlating with routine pulmonary clinic follow up and East and West Primary Care Follow up) where the following assessments will be recorded:

- Medication changes/refills (obtained through pharmacy record)

- FEV1, FEV1/FVC, FEF25-75 and FeNO per clinical standard of care (only assessed in the Pulmonary clinic)
- Child Asthma control test (ACT) questionnaire
- Serious Adverse Events will be recorded at each visit
- Missed school days
- PedsQL asthma module (patient and parent report)
- Test of Adherence to Inhalers
- Exacerbation of asthma episodes (obtained through self-report and chart review) requiring:
    - Doctor visits outside of standard of care
    - ER visits
    - Hospitalizations

In addition, active participants (test group) will be continuously monitored via the CoheroConnect dashboard which allows the Investigator to monitor the child's medication adherence in real time. If a period of participant inactivity of 3 days is registered in the system, the Investigator (or designee) will be notified and he/she will be prompted to contact the participant to remind them to take their medication as prescribed. The Investigator or designee will review patient specific data (% adherence since last visit and graph of adherence patterns over time since enrollment) through the CoheroConnect dashboard within two days before a follow up visit. At the follow-up visit, these data will be reviewed with the patient and parent/caregiver. The adherence rate and barriers identified will be discussed and, if necessary, personalized strategies for improvement will be devised. These data will also be shared with the clinician during these follow up visits. Medication adherence data for control participants will be obtained by measure of pharmacy record refill information and self-report (Test of Adherence to Inhalers) throughout the duration of the study.

We understand that the self-report of missed school days due to asthma may be unreliable and subject to recall bias, however, this is the method we currently use clinically to assess this measure.

If a participant is unable to complete the follow-up visit at their routine pulmonary appointment, the coordinator will either mail, text a link, or email a link of the follow-up surveys to the participants. They will be reminded 3 times via text, email or phone to complete the follow-up questionnaires.

8.5.End of Study Visit

Participants who finish the 180-day visit will be considered "complete". They will then be provided with a $35 gift card for completing the study and returning their devices (HeroTracker).

8.6. Participant Withdrawal

If premature withdrawal from the study occurs for any reason (including death) the investigator must determine the primary reason for withdrawal and record this information on the study

Withdrawal CRF. For participants who are lost to follow-up (i.e., those participants whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator will show "due diligence" by documenting in the source documents the steps taken to contact the participant, e.g., dates of telephone calls, letters, emails, etc. If the participant fails to respond after 3 attempts they may be withdrawn from the study.

8.7 Accrual and Study Duration

We anticipate enrolling 4-5 subjects/week through the pulmonary clinic at the Hartford and Farmington locations. The Pulmonary Clinic at CCMC sees 15-30 patients/day at the Hartford location with 75% of the children having a diagnosis of asthma (~10-20/day), half of whom will be in the desired age range (~5-10) and will be screened. We will focus recruitment efforts on 2 days per week when the greatest number of patients are scheduled. To minimize selection bias, we will vary the time of day and day of the week in which we recruit. Therefore, enrollment should take approximately 16 weeks to complete and the study will conclude 6 months after that last subject is enrolled.

9. ADVERSE EVENT REPORTING

This is a non-significant risk study exploring the use of the BreatheSmart System in the management of children who present with poorly controlled asthma symptoms despite being managed on inhaled corticosteroids.
For the purposes of this study, the following anticipated adverse events and those meeting the definition of serious must be reported.

9.1.Recurrent Exacerbation of Asthma

An exacerbation of asthma requiring an intervention by the investigator must be recorded. The occurrence of these events will be obtained through both self-report and chart review. These events include:

- change in/or addition of prescribed medications for the treatment of asthma, or
- doctor visits outside of standard of care, or
- ER visits, or
- Hospitalization

9.2.Adverse Drug Reactions

Adverse reactions to medications prescribed for the treatment of asthma are well described in the literature. If an event related to a prescribed asthma drug meets the definition of serious it must be reported.

9.3.Serious Adverse Event Definition

A serious adverse event or reaction is any untoward medical occurrence that:

- Results in death
- Is life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Results in a congenital anomaly/birth defect

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. The investigator will be responsible for assigning causality to all serious adverse events.

In the event that a SAE leads to hospitalization, every effort should be made by the investigational site to obtain the medical records/discharge summaries and complete a Hospitalization CRF.

9.4.Death

In the event that the SAE leads to death, the Investigator should provide a narrative summary of circumstances, the events related to the death, and the primary cause of death, if known. Information regarding a participant's death must be reported within 24 hours of the knowledge of the death, and recorded on a Mortality form.

10. DATA MANAGEMENT

Prior to study enrollment, all research staff will be trained in principles of human subjects protection and maintenance of confidentiality of participant data.

10.1. Data Confidentiality

Participants limited PHI and the investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor will take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

The investigator must take all appropriate measures to ensure that the protection of data for each study participant is maintained. The investigator, and all site staff involved in this study, may not disclose (or use for any purpose other than performance of the study), any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Cohero Health must be obtained for the disclosure of any said confidential information to other parties. All information recorded on CRFs must be traceable to source documents in the participant's research file and/or medical chart with the exception of participant questionnaires that are completed directly in BreatheSmart or Qualitrics.
Study data will be directly captured into BreatheSmart. Participants and study personnel requiring access to research systems will be trained and must use their own login and password. Access to clinical study information in these systems will be based on individuals' roles and responsibilities and the minimum rule. These applications provide hierarchical user permissions for data entry, viewing, and reporting options. For optimum security, all communications between the users and the applications operate on a secured socket layer (SSL) using 128 and

256-bit encryption. The web servers are protected by a managed firewall from potential web and network attacks, and the networks are guarded by an intrusion detection and protection surveillance system against malicious threats. These applications are designed to be in full compliance with International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's Code of Federal Regulations (CFR) Number 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials, the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and Subtitle D of the Health Information Technology for Economic and Clinical Health (HITECH) Act, 2009

10.2. Data Monitoring

All questionnaires will be administered using the Qualtrics HIPAA-compliant web-based data collection software and app presented on encrypted and password protected iPads. All surveys administered at each visit (including the TAI, PedsQL, baseline data collection form, and follow up data collection form) are built into the Qualtrics platform. Qualtrics is a HIPPA-compliant electronic survey development and analytic tool. All data collected through Qualtrics will be stored into a pass-word protected Qualtrics account. PHI will not be entered into the database. Upon enrollment, subjects will be designated a study number. Once data is entered in the database, they will only be identified by study number. All communications with enrolled participants will be documented in a password protected ACCESS database on password-protected and encrypted computers in the Asthma Center. No PHI will be entered into this database.

Original source documents including the original signed consent form, HIPPA form, and any other relevant documents will be kept in a locked filing cabinet in a locked office until data analysis is complete. The PI will be responsible for monitoring the quality of the CRF completion and source documents.

10.3. Data quality

10% of the records will be spot checked on three separate occurrences: after completion of all data entry for baseline visits, 90 day follow-up visits and end of study visits (180 days post randomization). The rate of error and location of errors will be recorded as de-identified data in an excel document.

10.4. Data analysis

All data will be analyzed in accordance with the statistical analysis plan (SAP) to be developed at the beginning of this study. Both primary and secondary analyses will be based on an intention-to-treat (ITT).
The study's primary objective is to estimate the relative improvement in medication adherence among children using the BreatheSmart compared to control participants using "standard of care".
Important secondary objectives include the extent to which the Cohero system improves:

- asthma control as measured by ACT

- FEV1, FEV1/FVC ratio, FEF25-75 and FeNO compared to standard of care, and the correlation between changes in medication adherence from baseline and changes in FEV1 and FEV1/FVC ratio.
- the overall number of provider visits for asthma-related adverse outcomes (number of exacerbations leading to Provider intervention, ER visits, hospitalizations, or requiring oral systemic corticosteroid therapy)
- Missed school days

Data results may be used to inform a study of a larger cohort with similar focus with regard to sample size estimates, efficacy of the BreatheSmart platform, feasibility in a low-income pediatric population and study design.

10.5. Statistical Analysis

Between group differences in the change in mean adherence from baseline over will be based on a 0.05 level t-test. The corresponding 95% confidence interval for the between group mean difference will provide an interval estimate of benefit obtained using the Cohero system. [NR1]

In addition to the frequentist analysis of adherence, a Bayesian approach that focuses on estimating the probability distribution of differences in mean adherence using the Cohero system compared to standard of care. The Bayesian approach begins with the premise that the Cohero system yields no improvement in adherence. This is an exact correspondence to a "null hypothesis". This assumption is incorporated through a prior distribution for improvement in mean adherence; for example, by assuming that the mean improvement is characterized by a normal distribution with mean 0, the expected difference should the Cohero system offer no benefit, and some small variance (e.g. 0.01). This is also a statement that the probability that the Cohero system improves response compared to standard of care is 50% (i.e., the prior odds that active therapy is effective is 1:1, consistent with the notion of equipoise).
The essence of the Bayesian approach is to use the data collected during the study to update the prior probability density based on the observed data (this updated density is the posterior probability distribution) using Bayes Theorem. This posterior distribution provides estimates of the probability that the Cohero system improves adherence relative to standard of care by any amount greater than δ. For example, choosing δ=0 corresponds to the frequentist test of the null hypothesis.
The analysis of lung function will be performed in a corresponding manner to that described for adherence. Additionally, the correlation between change in FEV1, FEV1/FVC ratio and FEF25-75 and change in adherence will be computed. Graphical analysis will be used to visually inspect the relationship between improvement in adherence and improvement in lung function. Based on the general form of the relationship, additional exploratory analyses will be performed. For example, if the relationship is approximately linear, standard regression methods will be used to estimate the relationship; if, however, a clear discontinuity is seen, splines might be used to estimate the relationship.

11.STUDY CONDUCT

11.1. Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be familiar with evidenced-based standard of care practice in the treatment of patients with asthma, the prescribing information of medications, and with the risks and potential benefits of the study. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master site files will be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

11.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at each participating institution will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the participants. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, recruitment advertisements (if applicable), written information given to the participants (including user manuals), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator or study sponsor.

11.3. Institutional Review

Prior to initiation this study must be approved by the CT Children's institutional review board (IRB) committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

11.4. Participant Information and Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risk Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR Part 46). They must be followed to comply with IRB regulations for the conduct and monitoring of clinical investigations. Freely given written informed consent must be obtained from every participant prior to clinical study participation.

11.5. Participant Confidentiality

In order to maintain participant privacy, all CRFs, study reports, and communications will identify the participant by the assigned alpha-numeric study number. Only study personnel will have access to the participant's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The participant's confidentiality will be

maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.6. Protocol Compliance

The investigator will conduct the study in compliance with this protocol and supporting documents. Any changes to the protocol will require approval from the IRB prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants. Any departures from the protocol must be fully documented in the source documents and the EDC.

11.7. On-site Audits

The IRB may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.8. Record Keeping and Retention

Data generated for the study will be stored in a limited-access file area and be accessible only to study personnel. All reports and communications relating to study participants will identify participants only by participant identification code. Complete participant identification will be kept by the investigator. This information will be treated with strict adherence to professional standards of confidentiality. An investigator must in reasonable time, upon request from any properly authorized officer or employee of FDA/relevant health authority or regulatory agency, permit such officer or employee to have access to requested records and reports, and copy and verify any records or reports made by the investigator. The investigator will also grant the representatives the same privileges offered to FDA/relevant health authority or regulatory agents/officers/employees.

11.9. Site Master File

The following documents will be retained in the site master file:

- Current signed curriculum vitae and medical licenses (within 1 year) for the Principal Investigator and all co-investigators.
- A copy of the IRB approval letter. Renewals must be submitted at annual intervals or as required by IRB policy.
- A copy of the IRB approved informed consent form
- IRB member list and DHHS General Assurance Number (FWA number).
- A fully executed clinical study agreement
- Signed Financial Disclosure Form
- The Investigator Protocol Agreement Form signed and dated by the Principal Investigator at each site.

In addition to the documents listed above, the PI will also retain the following items:

- All original informed consent forms with required signatures
- All IRB correspondence (i.e., informed consent [including any approved revisions], protocol, advertisements, newsletters)
- Training Logs
- Copies of all correspondence pertaining to the study between the Sponsor, Site and the Participants
- Study Monitoring Log
- Delegation of Authority Log
- Device Accountability Log

All study-related records must be maintained in accordance with local IRB policies. The investigator will not discard any records until completion of the study.

11.10. Study Report and Publication

The data resulting from this study may be published. A publications committee consisting of investigators, statisticians, and Cohero representatives will be convened to establish a publication policy.

REFERENCES

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Appendix 1
Table A
Pressurized metered dose inhaler (pMDI) compatible with the BreatheSmart HeroTracker

Daily Control	
Advair Diskus (100/50 mg), (250/50 mcg), (500/50 mcg)	Dulera 100/5 mcg and 200/5 mcg
Advair HFA (45/21 mcg), (115/21 mcg),	Duolin HFA 20 mcg

(230/21 mcg)	
AeroSpan 80 mcg (60 count) and (120 count)	Flovent 44 mcg, 110 mcg and 220 mcg
Alvesco 80 mcg and 160 mcg	Flovent Diskus 50 mcg, 100 mcg and 250 mcg
Asmanex HFA	Foratec HFA 12 mcg
Asthavent 100 mcg	Foster 100/6 mcg
Atimos 12 mcg (50 count), (100 count) and (120 count)	Ipvent HFA 40 mcg
Beclate HFA 50 mcg, 100 mcg, 200 mcg	QVAR 40 mcg, 80 mcg
Budeflam 100 mcg	Serevent Diskus
Ciclovent 160 mcg	Seroflo 50 mcg,125 mcg, 250 mcg
Clenil 50 mcg, 100 mcg, 200 mcg, 250 mcg	Symbicort 80/4.5 mcg, 160/4.5 mcg, 400/12 mcg
Rescue	
Atrovent HFA	
ProAir HFA	
Proventil HFA	
Ventolin HFA 60 count, 200 count	
Xopenex HFA 80 count, 200 count	