A Pilot Randomized Controlled Trial: Utilizing a Digital Inhaler Cap for Remote Asthma Management in Adolescents with Intellectual and Developmental Disabilities

A randomized, open label, 34-subject clinical trial of a digital inhaler in the treatment of asthma in adolescents with intellectual and developmental disabilities.

Study Chairperson or Principal Investigator:

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Cognita Labs®

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PRÉCIS

Study Title

A Pilot Randomized Controlled Trial: Utilizing a Digital Inhaler Cap for Remote Asthma Management in Adolescents with Intellectual and Developmental Disabilities

Study Objectives

Primary Objective: To evaluate the feasibility, acceptability, and usability of a remote home monitoring approach with daily CapMedic® medication reminders, used alongside the CapMedic® inhaler to objectively record inhaler use, and to explore whether this approach improves medication adherence at 4 and 8 weeks compared with control participants among adolescents with intellectual and developmental disabilities (IDD) and moderate-to-severe asthma.

Secondary Objective: To test lung function using one non-invasive low effort test fractional exhaled nitric oxide (FeNO), and one effort-dependent spirometry test (FEV_1 and PEF) at baseline, 4 weeks and 8 weeks between control and intervention group. Establish effect size and the variability of the low effort changes the fractional concentration of exhaled nitric oxide, and effort dependent FEV_1 and PEF at week 8 from baseline between intervention and control groups.

Tertiary objective: To explore whether medication adherence and inhaler technique score are associated with lung function.

The project will establish feasibility, acceptability, attrition, and protocol compliance for remote home use, and will collect pilot data needed for power calculations in preparation for an R01 Randomized Controlled Trial as a next step to test the effectiveness of the device in children with IDD and co-occurring moderate severe asthma.

Design and Outcomes

This is an open label, randomized controlled clinical trial to test the feasibility and acceptability and to establish the effect size of an intervention, use of the CapMedic® digital inhaler cap in adolescents with intellectual and developmental disabilities (IDD) and co-occurring moderate to severe asthma in adolescents ages 10-17.5 years of age.

Interventions and Duration

Control: Standard of care metered dose inhaler (MDI)/ hydrofluoroalkane (HFA) propellent + passive-mode CapMedic® digital inhaler cap during remote home use, and measuring inhaler proficiency technique, and measuring lung function in clinic in adolescents with intellectual and developmental disabilities (IDD) and co-occurring moderate to severe asthma; 8 weeks (baseline, week 4, week 8 visits).

Intervention: Standard of care MDI/HFA + active-mode CapMedic® digital inhaler cap during remote home use promoting daily CapMedic® medication reminders from REDCap to their text messages, measuring inhaler proficiency technique, and measuring lung function in clinic in adolescents with intellectual and developmental disabilities (IDD) and co-occurring moderate to severe asthma; 8 weeks (baseline, week 4, week 8 visits).

Sample Size and Population

Julios (2005), recommended a minimum sample size of 12 adolescents per group for a pilot study. Accounting for 36% attrition, based on our previous pilot study, we will need to recruit at least 17 subjects per group or a total of 34 adolescents.

STUDY TEAM ROSTER

Principal Investigator: Larry Yin, MD, MS

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Main responsibilities/Key roles: As PI, Dr. Yin will oversee all components of the study and will guide the team on all aspects of the recruitment / retention strategies, data collection protocols, and data analysis and dissemination for both qualitative and quantitative aspects of the research.

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Main responsibilities/Key roles: Dr. Deavenport-Saman will oversee and supervise the Project Coordinator's/CRC's/RA's activities, the recruitment and retention of the study participants, and will serve as the primary liaison with the biostatistician.

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PARTICIPATING STUDY SITES

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Main responsibilities/Key roles: Dr. Tam will oversee recruitment at CHLA Allergy and Immunology.

1 STUDY OBJECTIVES

1.1 Primary Objective

To evaluate the feasibility, acceptability, and usability of a remote home monitoring approach with daily CapMedic® medication reminders, used alongside the CapMedic® inhaler to objectively record inhaler use, and to explore whether this approach improves medication adherence at 4 and 8 weeks compared with control participants among adolescents with intellectual and developmental disabilities (IDD) and moderate-to-severe asthma.

Hypothesis 1: Feasibility will be measured by recruitment rate, retention rate, data completeness - the proportion of objective data generated by the CapMedic® inhaler cap for daily reminders. Acceptability will be measured by qualitative open-ended surveys; questions will be asked in terms of likability, perceived helpfulness, ease of use, and referral of the interventions to others. Surveys will also capture adherence and satisfaction.

1.2 Secondary Objective

To test lung function using one non-invasive low effort test fractional exhaled nitric oxide (FeNO), and one effort-dependent spirometry test (FEV_1 and PEF) at baseline, 4 weeks and 8 weeks between control and intervention group. Establish effect size and the variability of the low effort changes in the fractional concentration of exhaled nitric oxide, and effort dependent FEV_1 and PEF at week 8 from baseline between treatment and control groups.

Hypothesis 2: The intervention group using the active-mode CapMedic® digital inhaler cap will have improved lung function measured by lower concentrations of fractional exhaled NO, and higher values of FEV_1 and PEF, compared to the control group.

1.3 Tertiary Objective

Tertiary objective: To explore whether medication adherence and inhaler technique score are associated with lung function.

Hypothesis 3: The intervention group using the active-mode CapMedic® digital inhaler cap will have higher inhaler proficiency scores, which will be associated with improved lung function measured by lower concentrations of fractional exhaled NO and higher values of FEV_1 and PEF, The control group will have lower inhaler proficiency scores, which will be associated with less improvement in lung function.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Asthma is a common, chronic medical condition affecting about 1 in 12 children living in the United Stated (Pate et al., 2021). Children who learn adequate management of their asthma gain enhanced quality of life and a lower risk of morbidity and mortality while poorly managed asthma presents challenges to children's well-being and life-expectancy (Akinbami, 2006). Successful medical management of asthma involves children, under the direction of their caregivers, carrying out a set of instructions without direct oversight from physicians. A high level of adherence to these instructions is critical in supporting treatment effectiveness. Effectively managing asthma necessitates developing a specific executive function-related skill set that includes understanding triggers and treatment, employing proper inhaler medication technique, comprehending an Asthma Action Plan, utilizing a peak flow meter, accurately interpreting respiratory symptoms, employing spacer devices, and adhering to prescribed therapies. Available data suggest that individuals with IDD have significant challenges in managing asthma leading to increased morbidity and healthcare utilization (Weiss et al., 2018, Fujiura et al., 2018, Fujiura et al., 2018, Lunsky et al., 2019, Nicholson et al., 2022).

However, empirical research examining specific challenges of medication adherence for asthma in individuals with IDD is lacking. Remote home monitoring may identify factors that impact asthma control and help provide information about patterns of asthma (van der Kamp, 2020).

Medications used to treat asthma often rely on inhaler delivery of medication. Properly using an inhaler requires at least five steps for the individual to remember and carry out. Step 1 is to always shake the inhaler canister in preparation for delivering the medication; Step 2 is to correctly orient the inhaler; Step 3 is to ensure coordination of delivery of the medication and inhalation; Step 4 is to have a prolonged inhalation; and Step 5 is to hold breath for 10 seconds past inhalation. Mistakes at each of these steps can result in ineffective delivery of medication to the lungs during an asthma attack. Digital inhalers, which integrate sensors and mobile applications, reduce the burden of adherence in asthma management by providing real-time monitoring, reminders, and personalized feedback. However, limited research has explored the feasibility and effectiveness of smart inhaler technology in the IDD population that faces increased risks of poor remote home asthma management due to executive function challenges. Therefore, this study aims to evaluate the feasibility and efficacy of utilizing smart inhalers in adolescents with IDD and asthma for remote home management.

Monitoring asthma symptoms often includes patient monitoring of Forced Expiratory Volume in 1 second (FEV_1) and Peak Expiratory Flow (PEF). FEV_1 is the maximum amount of air that can be forcefully exhaled in one second after taking a deep breath. It is typically measured using a peak flow meter through a simple breathing test. A decrease in FEV_1 indicates airway obstruction and can suggest worsening asthma symptoms or an asthma exacerbation. Regular monitoring of FEV_1 can help individuals with asthma, their caregivers, and healthcare providers track changes in lung function over time and adjust treatment accordingly. PEF measures the maximum airflow rate achieved during a forceful exhalation, regardless of the duration of the exhalation. It is also measured using a peak flow meter. PEF values are influenced by various factors such as airway inflammation, bronchoconstriction, and triggers like allergens or exercise. Monitoring PEF on a daily basis, usually in the morning and evening, can help individuals with asthma identify patterns, detect early signs of worsening symptoms or asthma attacks, and take appropriate action, such as adjusting medication or seeking medical attention. Both FEV_1 and PEF are valuable tools in asthma management. They provide objective measurements of lung

function, allowing healthcare providers, individuals with asthma, and their caregivers to monitor changes, assess response to treatment, and make informed decisions to optimize asthma control and minimize the risk of complications.

Digital inhaler health systems use electromechanical sensors and microelectronics to monitor inhaler actuation as well as measure FEV_1 and PEF. These devices can be linked to a mobile application that communicates with the patient, a cloud server, and a portal for the physician to see dashboard data to help monitor asthma symptoms. Digital inhalers can also employ Bluetooth to detect inhaler usage, remind patients to take medication, and collect data to assist treatment. They can enhance patients' adherence to medication management instructions and keep their disease under control, but they must be created with health systems and individuals in mind to be effective.

The FeNO test is frequently used in clinical care for children with asthma. The most recent American Thoracic Society (ATS) update on using FeNO to guide asthma treatment in children and adults was published in 2021. It strongly recommends the use of FeNO testing in addition to regular care procedures for the management of asthma in patients (Dweiki et al., 2011, Khatri, 2021). In 2012, in response to the ATS guidelines, the American College of Allergy, Asthma and Immunology (ACAAI) and the American Academy of Allergy, Asthma and Immunology (AAAAI), published a joint statement: “We formally recognize and support the 2011 ATS Clinical Practice Guideline on the Interpretation of Exhaled Nitric Oxide for Clinical Applications” (Zit, 2017).

While this method may be easier than spirometry, especially for adolescents with IDD, it is not a substitute for spirometry or a pulmonary function test only useful in early childhood patients. Asthma management includes a combination of various techniques that complement one another, such as spirometry, impulse ocsillometry, fractional exhaled nitric oxide (FeNO), and plethysmography (Postma, et al, 2019).

2.2 Study Rationale

Managing medication administration and ensuring correct administration can be challenging for children, especially those with intellectual and developmental disabilities (IDD), including autism (Lunsky, 2018). The rate of incorrect inhaler administration is already high in the general population, accounting for 30-90% of patients with incorrect use[i,ii,iii,iv]. This results in decreased efficacy of controller medication[v]. Various studies have found that assistive electronic devices increase medication adherence in the pediatric population. For example, smart devices such as Turbu+, INCA, Digihaler, Respiro, Smart AeroChamber, and the Hailie, which track the duration of inhalation, frequency of usage, and/or spirometry data, have improved clinical outcomes such as medication adherence and lung functions[vi]. Given the high rate of incorrect administration, there has also been an effort to create home assistive interventions that promote correct administration. CapMedic is among the first smart inhaler devices to provide step-by-step real-time feedback on inhaler technique, and it has shown to enhance correct medication administration in the pediatric population[vii].

Despite representing approximately 15.0% of the U.S. children, the pediatric IDD population is underrepresented in medical research surveillance data[viii], and there is a lack of published research on asthma and its treatment in people with intellectual disabilities, including autism[ix]. There is a scarcity of empirical research that examines the specific challenges of medication adherence for asthma in individuals with IDD. Therefore, this study aims to investigate the impact of using smart inhalers in the ID/DD population for remote home management to improve the rate of correct medication administration and lung function, measured by effort dependent (spirometer) and a non-effort dependent test such as FeNO. This research is aimed

at promoting better asthma management and the prevention of exacerbations in the IDD population.

3 STUDY POPULATION

3.1 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study:

- Adolescents ages 10-17.5 years
- Diagnosis of mild-to-moderate intellectual disability (ID) ICD-10: F70-F71 and/or diagnosis of developmental disability, including autism: ICD-10: F80-89;
- Diagnosis of moderate-to-severe asthma or moderate or severe unspecified asthma or diagnosis indicated in the EMR: ICD-10: J45.40-J45.909;
- Parent/legal guardian is willing to answer questions about their child.
- Parent/legal guardian and adolescent must have the ability to understand study procedures and to comply with them for the entire length of the study
- English or Spanish-speaking participants
- Not currently involved in other studies using digital inhalers
- Males and females of reproductive capability will be enrolled: contraception is not necessary or required.
- Participants must use any of the following MDIs (as indicated by the 510(k) as maintenance inhaled corticosteroids (ICS): Advair HFA, Flovent HFA, Symbicort HFA, Alvesco HFA, Dulera HFA, and Asmanex HFA.

3.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation:

- Any clinical condition that limits life expectancy and complex respiratory pathologies (e.g., tracheostomy, restrictive lung disease, bronchopulmonary dysplasia, cystic fibrosis) that could confound asthma treatment outcomes.
- Inability or unwillingness of individual or legal guardian/representative to give written informed consent.

3.3 Number of Subjects

We will need to recruit at least 17 subjects per group or a total of 34 adolescents. We will randomly assign half of the recruited adolescents to either the Intervention Group or to the Control Group.

4 PROCEDURES INVOLVED

4.1 Study Design

Randomized-controlled, open label trial in adolescents with intellectual and developmental disabilities (IDD) and co-occurring moderate-to-severe asthma.

4.2 Description of Device

CapMedic® is an FDA-cleared smart inhaler that measures the correctness of inhaler use. CapMedic sits on top of the metered dose inhaler (MDI/HFA) and measures the four key steps of inhaler use: duration of inhaler shaking, orientation, coordination timing, and inhalation duration.

CapMedic® operates in two modes. In the "active mode", the device also provides interactive audio-visual guidance to remind the correct inhaler use during the dosage.

CapMedic® also has a silent feature where it only measures inhaler technique parameters but does not provide active feedback to the patient. This is referred to as "passive mode" CapMedic®. The device is put into passive mode remotely through the CapMedic portal, so participants can't accidentally go into active mode.

In this study, CapMedic® will be used solely for its standard, intended functions related to inhaler-technique measurement and feedback. The device will not be evaluated for performance, safety, or effectiveness, and no device-specific performance endpoints are being collected. CapMedic® will function only as an operational tool to support the study's feasibility, acceptability, usability, adherence, and inhaler-technique objectives related to remote home monitoring.

Although the CapMedic® device is FDA cleared to perform FEV_1 and PEF measurements, in this study it will be used only to record inhaler actuations, assess inhaler technique, and, when in active mode, provide audio and visual feedback on inhaler use. All lung function measurements, including FEV_1 and PEF, will be obtained using a separate spirometer as described throughout the protocol.

4.3 Randomization

Participants will be randomized using the REDCap randomization tool. The randomization date is the date all the screening criteria are met, and the family agrees to participate.

We plan for equal allocation (1:1) across study groups; the study statistician (Co-PI: Vu) will generate a randomization list with gender as stratification factor to ensure balance between groups. The study statistician will upload a "Development" randomization list and a separate "Production" randomization list into REDCap. The randomization lists are housed on CHLA's "OneDrive" with restricted access such that only unblinded individuals can access.

Intervention Group: Standard of care metered dose inhalers (MDI/HFA) + active-mode CapMedic® digital inhaler cap and medication reminders at home and during clinic visits.

Control Group: Standard of care metered dose inhaler (MDI/HFA) + passive mode CapMedic® at home and during clinic visits.

The only difference between the intervention and the control groups is that the intervention group receives the active-mode CapMedic® digital inhaler cap with the audiovisual cues and medication-reminder text messages delivered through REDCap in addition to the standard of care. The CapMedic® provided to the control group will be in passive mode and will not receive medication-reminder text messages at home and during clinic visits.

4.4 Medical Record Review

We will review medical records for: 1) verification of study eligibility after the phone screening 2) to verify the safety outcomes of adolescents, and 3) to obtain any missing data. All CHLA families will be asked to sign HIPAA forms.

Safety outcomes: See the data collection tool in the IRB application for the specific data points to be collected.

We have approval to obtain information from medical records via a data use agreement from AltaMed. All AltaMed families will be asked to sign HIPAA forms.

4.5 Interventions, Administration, and Duration

Control Group: Standard of care metered dose inhaler (MDI/HFA) + passive-mode CapMedic® digital inhaler cap on the inhaler proficiency technique, at home and during the clinic visit, in adolescents with intellectual and developmental disabilities (IDD) and co-occurring moderate to severe asthma; 8 weeks (baseline, week 4, week 8 visits).

Intervention Group: Standard of care metered dose inhaler (MDI/HFA) + active-mode CapMedic® digital inhaler cap at home and during clinic visits on the inhaler proficiency technique and CapMedic® and medication reminders in adolescents with intellectual and developmental disabilities (IDD) and co-occurring moderate to severe asthma; 8 weeks (baseline, week 4, week 8 visits).

Intervention and Administration: The participants will be randomized into control and intervention groups. The first visit will assess the baseline inhaler technique for all patients. The inhaler use technique will be measured in both groups using observational assessment as well as the CapMedic® device. The total score will be computed using the inhaler proficiency schedule (IPS) scale combined with the CapMedic® output of four parameters namely inhaler shaking duration, orientation, coordination timing, and inhalation duration. The CapMedic® provided for baseline measurement is in passive mode, which does not provide any feedback to the patient but measures the four-parameter inhaler technique. Also, placebo MDI inhalers will be used for training, so no medication will be administered during the clinic visits.

Remote home monitoring

Remote home monitoring will be conducted in both intervention and control groups for the 8 weeks of the study. Both groups will take the device home and will be monitored by the CHLA study team based on their use of the CapMedic device, with the intervention group using the active mode, which provides audio-visual feedback, and the control group using the passive mode, with no feedback. In addition to device-based monitoring, the intervention group will also receive medication-reminder text messages through REDCap. Through remote home monitoring, we will be able to remotely and objectively understand inhaler use technique.

Remote home monitoring will entail three primary steps: 1) Easy Setup and Onboarding, 2) 15-minute coaching session and 3) Automated Data transmission.

1) Easy Setup and Onboarding:

- Cognita provides the capacity for CHLA to remotely set-up the CapMedic device for the intervention and control groups. Those in the control group will have the device remotely set to passive mode, while those in the intervention group will be set to active mode. The CHLA study team will log-in to Cognita's portal to ensure the CapMedic device number has the correct RedCap ID number in order to accurately link information to each adolescent. Cognita will have access only to coded device data and will have no access to the linkage file maintained by CHLA.

2a) Intervention group: 15-minute virtual coaching session at baseline and daily check-ins via text:

- **Cognita Labs** will conduct 15-minute virtual coaching session for families in the intervention group at the baseline visit to train them on proper inhaler use, using the

CapMedic device, after the CHLA team documents the baseline IPS scores during the baseline visit. During this session, they do not receive any identifiable information about the families, including, name, phone number, or email. Cognita will provide CHLA access to the data portal. The CapMedic device syncs to the Cognita Labs portal, which is a secure coded portal/database.

- **CHLA research team**: will be responsible for the remote home monitoring. Remote home monitoring is defined as tracking use of the CapMedic device attached to their daily inhaler medication, while the adolescent is at home. The purpose of home monitoring in the present study is to capture daily inhaler proficiency data from the device attached to the adolescents' inhalers, so they don't have to come in CHLA every day. **We will send automated, daily medication reminders via RedCap**. The CHLA research team will monitor the portal every 1-2 days. If the Cognita Labs portal indicates that adolescents don't use their inhalers for two days, the CHLA research team will reach out one time via a phone call to remind their parents to have their adolescents use their inhaler, along with the device and will answer any questions related to inhaler use proficiency. If the parent does not pick-up, the team will leave a message reminding them to use their inhaler, along with the device and will provide contact information if the parent has any questions related to inhaler proficiency use.

2b) Control group: CHLA will provide standard of care asthma education on how to use an inhaler after documenting the baseline, 4-week, and 8-week IPS scores during each visit. CHLA will passively collect data into the portal for the control group to understand their inhaler proficiency score at home. This will allow us to compare outcomes in the intervention vs. control group.

3) Automated Data Transmission: Coded data collected from the CapMedic device for both intervention and control groups will automatically sync over Wi-Fi/cellular networks to the Cognita secure coded password-protected portal. CHLA will download the coded weekly data to enter it into REDCap for future analysis. Cognita labs will not have any access to HIPAA related information for adolescents or parents, including the link to identifiable information.

Cognita's Role in Data Handling and Analysis
Cognita will have access only to coded device data through the CapMedic portal and will have no access to the linkage file maintained by CHLA. Cognita will not use participant data for any purpose outside of this study. Cognita does not generate any metrics, summaries, or analytic outputs for CHLA and does not conduct any data analysis or interpretation for study outcomes. Cognita may review coded device data from the intervention group solely for the purpose of training the CHLA study team on optimal use of the CapMedic device in active mode, which is the only mode that generates audiovisual feedback and requires device-specific operational guidance. All data analysis, interpretation, and generation of study metrics will be conducted exclusively by CHLA.

No access to Home Wifi: Snycing the data at home
For the intervention and control groups, it does not matter whether the device is in active or passive mode, as the CHLA team still needs to access their data that has been scyned from the device to the portal. We will train families to remember to charge the CapMedic device at home, and will teach families how to use the home Wi-Fi hub, if they don't have access to home Wi-Fi, which will allow the data to sync from the CapMedic devices to the secure password protected portal with coded data. Only the CHLA study team and Cognita will have access to the coded

data portal. Cognita will have access only to coded device data and will have no access to the linkage file maintained by CHLA.

Next, for each visit, the control group will receive standard-of-care instructions on correct inhaler use while the intervention group will receive live/active feedback from the CapMedic® device for correct inhaler use. The CapMedic® provided to the control group is in passive mode. The CapMedic® provided to the intervention group is in active mode and provides audio-visual feedback to participants during inhaler use while also measuring the inhaler technique.

The intervention will be administered by Dr. Deavenport-Saman, Dr. Dos Santos, Dr. Solomon, and research assistants, who have been added to iStar, whether the families are from CHLA or AltaMed sites. The study is free to participants whether the families are from CHLA or AltaMed sites.

We anticipate that the baseline visit for intervention and control groups will take up to:

- Baseline visit: 1.5 hours: Consent and enroll in the study, randomize to the intervention, or control group, provide the brief training with CapMedic device, observe and measure actual inhaler proficiency technique, measure FEV_1 and PEF using a spirometer, and conduct fractional exhaled nitric oxide (FeNO) test and complete surveys (See 4.8 Schedule of Evaluations), and provide gift card. There is a CapMedic portal that will log inhaler proficiency technique as measured by the device at home and during clinic visits for intervention and control groups.

- 4-week visit: 45-60 minutes: observe and measure actual inhaler proficiency technique, measure FEV_1 and PEF using a spirometer, and conduct fractional exhaled nitric oxide (FeNO) test, and complete surveys (See 4.8 Schedule of Evaluations) and provide gift card. There is a CapMedic portal that will log inhaler proficiency technique as measured by the device at home and during clinic visits for intervention and control groups.

- 8-week visit: 45-60 minutes: observe and measure actual inhaler proficiency technique, measure FEV_1 and PEF using a spirometer, and conduct fractional exhaled nitric oxide (FeNO) test, and complete surveys (See 4.8 Schedule of Evaluations) and provide gift card. There is a CapMedic portal that will log inhaler proficiency technique as measured by the device at home and during clinic visits for intervention and control groups.

4.6 Survey(s)/Questionnaire(s) and Device Measures

All surveys will be completed on REDCap. The Observer rating of the IPS is the only one that is validated.

- Observer rating Inhaler Proficiency Technique of adolescents' use of inhaler shaking duration, orientation, coordination, and inhalation duration. Correctness of use: includes device and observer ratings.
    - We created the IPS-IDD based on previously validated questionnaires measuring inhaler proficiency and the CDC guidelines:
    - 1. Mac Hale E et al (2014), Inhaler Proficiency Scale (IPS) (10-item) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5047302/
    - 2. Lizano-Barrantes et al (2022), The Inhaler Technique Questionnaire (InTeQ) (5-item) https://pubmed.ncbi.nlm.nih.gov/35270283/
    - 3. CDC guidelines (10-item):

https://www.cdc.gov/asthma/pdfs/inhaler_in_mouth_factsheet.pdf

- Demographics Survey (Parent- and Adolescent-reported): Family/Adolescent Characteristics (age, sex, race, ethnicity, etc.)
- Clinical outcomes (measured in adolescent):
    - CapMedic device measurement of daily use. Adherence: Used at least once per day (yes/no)
    - CapMedic device measurement of Inhaler Proficiency Technique: Total score out of 4
    - Forced expiratory volume (FEV_1): indicates amount of air that a person can force out of their lungs in 1 second, as measured by a spirometer.
    - Peak Expiratory flow (PEF) rate indicates how quickly a person can blow air out of their lungs as measured by spirometer.
    - Fractional exhaled nitric oxide (FeNO): measures the amount of nitric oxide exhaled from a breath. Higher levels of nitric oxide are associated with inflammation of lung airways. Among adolescents taking inhaled corticosteroids (ICS), the results will show how effective the medications are.
- Feasibility will be assessed by recruitment rate, retention rate, number of days participants use their inhaler (adherence)
    - Motivation Medication Adherence (Parent and Adolescent): Measures self-report of motivation to use inhaler and medication adherence.
- Acceptability and usability were measured at W4 and W8 via study-specific self-reported surveys developed with input from behavioral health specialists to ensure appropriateness and ease of understanding for the IDD population. Acceptability was defined as the degree to which participants perceived the intervention as appropriate and satisfactory.20 Satisfaction was assessed via a face-valid 5-star rating item [Perski and Short, 2021] and a 5-point Likert scale (ranging from 'very unsatisfied' to 'very satisfied'). Motivation for daily use was assessed on a 3-point scale (not motivated at all, somewhat motivated, very motivated). Usability was defined as the extent to which the device could be used effectively and with ease.21 It was measured by participant-reported confidence in correct inhaler use on a 5-point scale (ranging from 'not confident' to 'very confident'). Additionally, participants in the intervention group were asked about their interest in receiving daily smartphone feedback using a 3-point scale. Finally, adherence was assessed via multiple-choice categories asking participants to estimate their medication use over the past week and month (0-25%, 26-50%, 51-75%, 76-100%).Satisfaction and Confidence (Parent- and Adolescent-reported): Measures self-report of satisfaction, usability, and confidence. Adapted from Perski and Short, 2021, using a and a 5-point Likert scale (ranging from 'very unsatisfied' to 'very satisfied'). Participant-reported confidence in correct inhaler use on a 5-point scale (ranging from 'not confident' to 'very confident').
- Safety outcomes (Parent-reported): urgent care visits, ED visits, inpatient visits.

4.7 Study Timelines

- Period of 8 weeks

4.8 Schedule of Evaluations

Assessment	Baseline, Enrollment, Randomization: Visit 1 (Week 1)	Visit 2 (Week 4)	Final Visit (Week 8)	All Weeks (1-8)
Enrollment/Randomization	X			
Informed Consent Form	X			
Demographics (Parent and Adolescent)	X			
Clinical outcomes (Adolescent)	X	X	X	
Inhaler technique (Adolescent)	X	X	X	
Motivation Medication Adherence (Parent and Adolescent)	X	X	X	
Satisfaction and Confidence (Parent and Adolescent)		X	X	
Safety outcomes (Parent)		X	X	
Home Smart Inhaler Use				X

Note: All assessments will be collected for both intervention and control groups.

Weeks 1-8: Remote home use

- CapMedic device measurement (device-generated): Used at least once per day (yes/no)
- CapMedic device measurement of Inhaler Proficiency Technique (device-generated): Total score out of 4 mean (SD), daily from baseline to week 8.

Visit 1: Baseline Assessments

- Demographics Survey (Parent- and Adolescent-reported): Family/Adolescent Characteristics (age, sex, race, ethnicity, etc.)
- Observer rating Inhaler Proficiency Technique (observer-rated): of adolescents' use of inhaler shaking duration, orientation, coordination, and inhalation duration.
- CapMedic device measurement of Inhaler Proficiency Technique: Total score out of 4
- Clinical outcomes (measured in adolescent): FEV_1, PEF, fractional exhaled nitric oxide level
- Motivation Medication Adherence (Parent- and Adolescent-reported)

Visit 2: 4 weeks

- Observer rating Inhaler Proficiency Technique (observer-rated): of adolescents' use of inhaler shaking duration, orientation, coordination, and inhalation duration.

- Clinical outcomes (measured in adolescent): FEV_1, PEF, fractional exhaled nitric oxide level
- Motivation Medication Adherence (Parent- and Adolescent-reported)
- Satisfaction and Confidence (Parent- and Adolescent-reported)
- Safety outcomes (Parent-reported)

Visit 3: Final Visit: 8 weeks

- Observer rating Inhaler Proficiency Technique (observer-rated): of adolescents' use of inhaler shaking duration, orientation, coordination, and inhalation duration.
- Clinical outcomes (measured in adolescent): FEV_1, PEF, fractional exhaled nitric oxide level
- Motivation Medication Adherence (Parent- and Adolescent-reported)
- Satisfaction and Confidence (Parent- and Adolescent-reported)
- Safety outcomes (Parent-completed)

4.9 Adherence of Assessment

Feasibility will be determined by data completeness and include the proportion of data obtained from the inhaler that can be obtained through 80% for each of the four key steps of inhaler use: duration of inhaler shaking, orientation, coordination timing, and inhalation duration.

- Primary outcome: Feasibility (recruitment rate, retention rate), acceptability (satisfaction), usability (confidence in ability to use device) for remote home monitoring; changes medication adherence (yes/no) for least one time per day at 8 weeks compared with control participants.

- Secondary outcomes:
  - FEV_1 (Forced expiratory volume in 1 second)
  - PEF (Peak expiratory flow):
  - Fractional exhaled nitric oxide (FeNO):
    - <20 ppb in children: Normal FeNO
    - 20-35 ppb in children: is considered an intermediate range: Numbers in this range should be matched with the medical history and testing
    - Over 35 ppb in children, up to 200 ppb) are considered high and indicate airway inflammation

- Tertiary outcomes:
  - Adherence and association with lung function (FEV_1, PEF, FeNO)
  - Observer Inhaler proficiency score (IPS): total out of 4: on shaking, orientation, coordination, and inhalation duration, measured by CapMedic® digital inhaler cap and association with lung function (FEV_1, PEF, FeNO)
  - Device IPS score and association with lung function (FEV_1, PEF, FeNO)

- Total Inhaler Use Competence = Shaking (≥ 5 seconds) + Orientation (Upright) + Coordination (> 0 seconds) + Duration (≥ 3 seconds) = score out of 4.
  - Shaking: Measures duration of shaking in seconds (continuous variable).
  - Orientation: Orientation of inhaler (+spacer assembly) measured as upright or not upright (binary variable)
  - Coordination: Time difference (in seconds) between the start of inhalation and medication actuation (continuous variable).

- Duration: Measured as inhaled duration (in seconds) post actuation (continuous variable).

Observation of Inhaler Use by Pediatrician	**CapMedic Analog**
Does the patient shake the inhaler for 5-10 seconds prior to use? **(Preparation/shaking) (CDC)**	**Measures duration of shaking in seconds. Correct shaking ≥ 5 seconds**
Does the patient place the inhaler in the spacer device? **(Preparation/shaking) (CDC)**	Detected automatically as there'll be no airflow (inhalation) detected if the inhaler cap is not removed before use.
Does the patient hold the inhaler between the index finger and thumb? (orientation) (CDC)	Finger grooves on the CapMedic result in patients intuitively holding the inhaler between their index finger + middle finger and thumb. Note that most inhalers are too rigid for children to actuate with just the index finger on one end.
Does the patient hold the spacer device and inhaler in a horizontal position? **(orientation)** (IPS #Q4)	**Orientation of inhaler (+spacer assembly) measured as upright or not upright (binary variable)**
Does the patient take a deep breath in, then breath out, and then put the spacer + inhaler in front of their mouth? **(coordination)** (IPS #Q5) (InTeQ #Q1)	Not detected by CapMedic but tied to duration step. This step is to achieve long slow inhalation which is detected by CapMedic. To get a full 3+ seconds of duration post-actuation, the patient needs to learn to breathe out first. Therefore, it can be tied to the duration measured by CapMedic. If duration >3 seconds, the patient likely exhaled fully before the inhaler puff. This step is part of the initial training to ensure that patients can inhale for at least 3 seconds post-actuation.
Does the patient place the spacer between their teeth and place their lips around the mouthpiece (coordination)	Not detected but poor seal will lead to low/no airflow measurement by CapMedic and marked as incorrect technique for either coordination or duration parameter. Also, note that coordination generally refers to the coordination of inhalation with medication actuation. With this definition, **CapMedic measures coordination as the time difference (in seconds) between the start of inhalation and medication actuation.** **Correct coordination > 0 seconds.**
Breath in as deeply as possible? (Duration) (IPS #Q6) (InTeQ #Q2, 3)	**Measured as inhaled duration post actuation (in seconds)** **Correct duration ≥ 3 seconds.**
Does the patient hold their breath for 10 seconds? **(Duration)** (IPS #Q7) (InTeQ #Q4)	CapMedic gives reminder feedback to "Hold your breath" but <u>does not detect if the step was performed.</u>
Does the patient breathe out slowly through their mouth? **(Duration)** (IPS #Q8) (InTeQ #Q5)	Not detected.

5 RECRUITMENT METHODS

5.1 Recruitment Strategies

- We are obtaining a list of potentially eligible participants from providers as referrals. We are the ones enrolling them into the present study.
- Physicians will refer patients to the study; families can also self-refer from flyers in clinic.
- To be eligible to participate, the participants must meet the inclusion criteria at least 7 days prior to week 1. Enrollment is defined as the time written informed consent is obtained.

Recruitment Pathway 1: CHLA clinics recruitment and enrollment procedures:
Dr. Yin, Dr. Park, Dr. Deavenport-Saman will provide a list of patients who meet the inclusion criteria for age, intellectual or developmental disability, and moderate-to-severe asthma status based on EMR review. Families may also learn about the study through flyers available in the clinic. These flyers will include study team contact information only and will allow families to self-refer by contacting the study team directly. Whether a family is identified through EMR review or contacts the study team after seeing a flyer, the Parent Phone Screener will be administered to confirm interest in participation and to collect eligibility information not available in the EMR. Families will not self-screen, and no QR code or electronic self-screening mechanism will be used. After completing the phone screener, families who appear eligible will be provided information about the study and invited to discuss participation further if interested.

Recruitment Pathway 2: AltaMed recruitment and enrollment procedures:
Dr. Yin, Dr. Delgado, or Dr. Park will provide a list of patients who meet the inclusion criteria for age, intellectual or developmental disability, and moderate-to-severe asthma status based on EMR review. Families may also learn about the study through flyers available in the clinic. These flyers will list contact information for the study team and allow families to self-refer by reaching out directly. Whether a family is identified through EMR review or contacts the study team after seeing a flyer, study staff will administer the Parent Phone Screener to confirm interest in participation and to collect eligibility information not available in the EMR. Only after completing the phone screener will families receive additional details about the study and be offered the opportunity to discuss participation further if they wish.

5.2 Screening for Eligibility

- Screening Evaluation: Eligibility is assessed through the Parent Phone Screener to establish potential eligibility, followed by EMR confirmation of required diagnoses to establish final eligibility.
- Screening Process: If recruited from flyer, participants have the option to call or email the study team to see if they are eligible to participate. All potential participants—whether identified through EMR review or through self-referral—will complete the Parent Phone Screener.
- We will maintain a coded screening log to determine reasons for ineligibility and to avoid recontacting the families. We will also need to generate a CONSORT diagram of those who were ineligible for clinialtrials.gov and for publication purposes. The information will be retained for study record keeping purposes per institutional policy. Coded Identifiers will be maintained only until the study is completed. After that, the identifiers will be

shredded and electronic records purged. The survey and data pulled from the EMR will be de-identified after the study is completed for up to 6 years.

- At least one week before enrollment, we will administer the Parent Phone Screener to establish potential eligibility and will confirm diagnoses in the EMR to establish final eligibility before scheduling families for in-person consent.

  A separate survey excel file will be coded and will link to a participant screener ID in the RedCap screening form.

  - We will ask the following questions on the screening form, which is located under surveys in iStar 21.2. All responses will be coded following data collection:

  1) Preferred Language English/Spanish
  2) Do you have a child between the ages of 10-17.5 years?
  3) Has your child been diagnosed with asthma?
  4) Has your child been diagnosed with an intellectual developmental disability, such as Down Syndrome or autism?
  5) Did your physician prescribe an inhaler medication to use daily?
  6) What is the name of your daily inhaler medication? Advair (Fluticasone/Salmeterol)
     - Advair (Fluticasone/Salmeterol)
     - Flovent (Fluticasone)
     - Symbicort (Budesonide/Formoterol)
     - Alvesco (Ciclesonide)
     - Dulera HFA (Mometasone/Formoterol)
     - Asmanex (Mometasone)
     - Other
  7) If you selected "other", what daily medication do you use?
  8) Do you currently own a spacer?
  9) May our colleague call you to learn more about the asthma study?
  10) How did you hear about the study?
     - Flyer
     - My doctor told me about it
     - From a friend
     - Other
  11) If you selected “other,” how did you hear about the study?
  12) Are you interested in having your child participate in our asthma study?

After answering questions on the screening form, potential participants can provide their contact information with some information being optional: The form will say please provide at least a phone number and/or email address where we can reach you.

1) Parent Name (optional)
2) Phone Number
3) Child Name (optional)
4) Email Address

In cases where parent-reported information and EMR documentation do not align, EMR documentation will serve as the definitive source for determining eligibility. Parent report during the phone screener will be used only to identify potentially eligible participants. If a parent reports a diagnosis that is not reflected in the EMR, the participant will not be considered eligible. If EMR documentation is incomplete or unclear, eligibility will not be established and the participant will be considered ineligible at that time.

Access to Identifiable Screening data:
See 2.1 in iStar application: Study personnel All RAs, PI (Dr. Yin), and Co-Is (Dr. Deavenport-Saman, Dr. Delgado, Dr. Mirzaian, and Dr. Dos Santos and My Vu) will have access to identifiable information to ensure that individuals who previously screened out are not re-contacted or re-approached about the study.

Retention and Identifiability of Screening Data:
The participant screening form will be coded. This will help to ensure that we do not recontact the same participants during the study. We also need to retain the information during study, as we need to generate a CONSORT diagram of those who were ineligible for clinialtrials.gov and for publication purposes.

5.3 Concomitant Interventions
This is consistent with the medications and interventions restrictions in the inclusion/exclusion criteria.

- Allowed Interventions: Other medications are allowed while enrolled in the study.
- Required Interventions: The active CapMedic® device is the only required intervention.
- Prohibited Interventions: Participation in other studies is allowed only if they do not involve other digital inhalers.

6 CONSENT AND HIPAA AUTHORIZATION

6.1 Obtaining Consent/Permission/Assent

- Consent procedures: Children with mild-to-moderate intellectual or developmental disability and with co-occurring moderate-to-severe asthma are eligible to participate in the study based upon their ability to comprehend the training on proper asthma inhaler technique. If there is a question regarding developmental disability or asthma status, we will review the EMR. All consent documents will be signed by parents, and assent documents will be signed by adolescents.
- Randomization procedure: After the consent forms are signed, the participants will be randomized to either the intervention or control group in REDCap.
- The measures that will be taken to ensure that subjects have sufficient time to consider participation: (e.g., they will be given an adequate amount of time to consider participation in the study relative to the initiation of study procedures, they will be allowed to review the consent form before coming in-person to participate in the study, take the informed consent document home to discuss participation with their family, friends, and/or others before making a definitive decision, etc.).
- The process for obtaining and documenting consent/permission/assent, and whether you will be following *"SOP: Informed Consent Process for Research (HRP-090)"* and *"SOP: Written Documentation of Consent (HRP-091)."*
- The role of the individuals listed in the IRB application as being involved in the consent process (This information will be required within the IRB application).
- Minor Subjects: Assent will be obtained from all minor subjects. Children with mild-to-moderate intellectual or developmental disability and with co-occurring moderate-to-severe asthma are eligible to participate in the study based upon their ability to comprehend the training on proper asthma inhaler technique. If there is a question regarding developmental disability or asthma status, we will review the EMR. Permission from the parent(s)/legal guardian(s) will also be obtained.

Parents and adolescents will consent and assent to participate in the study. All participants must sign the consent or assent forms.

Both the PI, Co-Is and research assistants have human subjects research training, good clinical practices training, and HIPAA certification. The PI and Co-Is will review any needed and necessary changes in the consent forms with the research assistants after approval of a study amendment.

A signed consent form will be obtained from each parent and will be available in both English and Spanish. A signed assent form will be obtained from each adolescent and will be available in both English and Spanish. The hard copies of these consent forms will be securely stored under lock and key in a secure CHLA office. Because our inclusion criteria include only mild-to-moderate intellectual disability, there are no participants who are anticipated to be unable to consent for themselves. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian, and this fact will be documented in the participant's record.

6.2 Research HIPAA Authorization

At CHLA, a partial waiver of HIPAA authorization is necessary, as CHLA personnel will access AltaMed PHI to identify, screen, and/or recruit AltaMed patients/records. We will obtain HIPAA authorization from all participants from CHLA and AltaMed. HIPAA authorization will be obtained from the adult subject or from the parent/legal guardian for minor subjects.

7 RISKS TO SUBJECTS

The risk of participating in the study is no greater than minimal risk of ordinary everyday activities.

Spirometry: You may feel short of breath or dizzy for a few moments after breathing into the spirometer.

Surveys: Risks associated with this research include potential loss of privacy, and discomfort experienced by adolescents in the study reflecting on their IDD and asthma status and the health conditions that they may face. It may provoke adolescents and their parents to experience difficult or emotional reflection on their current situation and past experiences of stigma, bullying, or discrimination.

Confidentiality: As this study involves the use of identifiable, personal information, there is a chance that a loss of confidentiality may occur. The researchers have procedures in place to lessen the possibility of this happening.

We will inform all participants that if they need to go to the emergency room, they should go without needing to contact anyone.

8 POTENTIAL BENEFITS TO SUBJECTS/SOCIETY

- There are no direct benefits to individual subjects of participating in the study.
- The study provides education on proper inhaler use technique and thus, participants may improve their knowledge and inhaler use technique.
- There may be indirect benefits to society in the future.

9 COMPENSATION

Describe the following:

- Participants will receive a $50 gift card for each visit attended.
- Payments will be made immediately after the visit in the form of a gift card.
- Participants will receive a $25 gift card for using the smart inhaler each day for 75% of the time or 6 weeks out of 8 weeks (42 days out of 56 days) of the study.
- They will also receive free parking at CHLA or AltaMed.
- Payments will be made immediately after the visit in the form of a gift card.
- Parents will receive the gift card on behalf of the child.

- Rationale for compensation: There is a body of research on financial incentives for adherence for asthma medication, especially in children and vulnerable populations (See studies below). We are tracking their daily use so it should not be a problem to determine whether they participated 6 weeks out of 8 weeks (42 days out of 56 days).
- Kenyon, C. C., Quarshie, W. O., Xiao, R., Yazdani, M., Flaherty, C. M., Floyd, G. C., Miller, V. A., Bryant-Stephens, T. C., Zorc, J. J., & Feudtner, C. (2025). Tailored Adherence Incentives for Childhood Asthma Medications: A Randomized Clinical Trial. *JAMA pediatrics*, *179*(5), 500–507. https://doi.org/10.1001/jamapediatrics.2025.0010

- Children's Hospital of Philadelphia, PolicyLab. *Tailored Adherence Incentives for Childhood Asthma Medications (TAICAM): Using Incentives and Mobile Health to Improve Medication Adherence for Children with Asthma* [online]. Available at: **http://www.policylab.chop.edu**. https://policylab.chop.edu/project/tailored-adherence-incentives-childhood-asthma-medications-taicam-using-incentives-and

- Hine J, Lee B, Bush A*, et al.* Patient financial incentives to improve asthma management: a systematic review *BMJ Open* 2023;**13:**e070761. doi: 10.1136/bmjopen-2022-070761

- Incentives for Adherence in Adolescent Asthma. https://clinicaltrials.gov/study/NCT03515499

10 DATA MANAGEMENT AND CONFIDENTIALITY

10.1 Data Collection Forms

The Co-Is or research assistants will collect data for each participant. Confidentiality of participant records will be maintained in accordance with CHLA IRB policy.

10.2 Data Management

Data will be collected and managed by the PI, research Co-Is and assistants. The study uses two data collection platforms: 1) REDCap, a HIPAA compliant platform that's secure and password protected; 2) CapMedic® data of the objective inhaler proficiency technique. Initial screening data and all study data (coded screening data, survey data and EMR data, and Cognita Labs portal data) will be labeled with a code that the research team can link to personal identifying information. (Coded). Cognita is not able access any identifiable information about study participants, as they do not have access to the link between identifiable information and the study ID numbers. The CHLA study team will log-in to Cognita's portal to ensure the CapMedic device number has the correct RedCap ID number in order to accurately link

information to each adolescent. Cognita will have no access to any HIPAA identifiers. Upon completion of the study, Cognita will delete all of the coded data from the portal. Upon completion of the study, CHLA will de-identify all data and the link will be destroyed.

Additionally, an MS Excel file contains information with the family names and study ID numbers. Another MS Excel file contains attendance and attrition for each participating family. Both files are located on a secure password protected CHLA server.

10.3 The CHLA research site will serve as the Data Coordinating Center Quality Assurance

10.3.1 Training

All study staff go through CITI and HIPAA certifications. All senior members of the research team have good clinical practices (GCP) training. The research assistants receive training on program content and study procedures at the start of the project. CapMedic® will also provide training for all Co-Is and assistants training the study participants.

10.3.2 Quality Control Committee

Co-Is and RAs will periodically review the data in weeks 4 or 6.

10.3.3 Metrics

Quality control metrics for outcome measures include clinical measures (FEV_1, PEF, FeNO, and inhaler proficiency technique)

10.3.4 Protocol Deviations

Report of protocol deviations will be reported to the IRB, within 48 hours of being identified.

10.3.5 Monitoring

Every quarter the Co-Is: Dr. Park and Dr. Deavenport-Saman and the research assistants will hold internal “data audits” to examine collected data for completeness and accuracy and to establish protocol compliance, data quality at the clinical sites, including review of records, and completion of consent forms. A summary of the “data audit” will be reported to the PI, Dr. Yin.

10.4 Participant Confidentiality

All adult participants will sign a HIPAA form. Surveys (See 4.8 Schedule of Evaluations) will be collected through a link in REDCap. Other baseline measurements are already entered in the medical record as part of a clinical visit. Inhaler proficiency technique will be collected via the CapMedic® device. FEV_1 and PEF will be collected via a spirometer. FeNo level will be collected. Due to any technological limitations, the research assistants will interview the participants and enter their replies in REDCap. A unified family ID will be used to link all data types.

Any data, forms, reports, and other records that leave the site will be identified only by a participant identification number (Family ID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using FIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the NICHD, and the OHRP.

10.5 Institutional Review Board (IRB) Review

This protocol and the informed consent and assent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. The consent form is separate from the protocol document.

10.6 Study Discontinuation

The study may be discontinued at any time by the IRB, the NICHD, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

11 FUTURE USE OF DATA

Use of Data for Future Research: Overall, the data collected as part of this study will be "coded". However, after study is completed the coded screening data, survey data and EMR data, and Cognita Labs portal data will be de-identified and may potentially be used for future research for up to 6 years. This means that there will be no way to link the data back to participants. Once the data have been de-identified, they may be used by the researcher conducting this study, the study sponsor, or other researchers (at CHLA or elsewhere) for future research projects that are unrelated to the purpose of this study.

12 WITHDRAWAL OF SUBJECTS

Researchers may end a subject's participation in this study for a number of reasons, such as, for the safety and welfare of the subject, if the subject does not follow instructions or if they miss scheduled visits. The researchers or the study sponsor might also decide to stop the study at any time.

Subjects may withdraw voluntarily from participating in the study at any time and for any reason. If a participant decides to stop being in this study, or is removed from the study, or the study is stopped, the researchers will ask the family whether they want to fully withdraw or partially withdraw. Some families may not be able to attend the in-person visit in person, but they may still be interested in completing the surveys. The researchers may call the subject and ask them and/or their parent if they want to complete any surveys that were not completed during the 2nd or 3rd study visit (depending on when they stopped study participation). The surveys include questions about medication use, satisfaction and confidence using the inhaler cap, and questions about urgent care visits, emergency department visits, and hospitalizations. Completing any additional surveys after you stop participating in the study is optional.

13 SAFETY ASSESSMENTS

13.1 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention. (asthma attack)

A **serious adverse event (SAE)** is generally defined as 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 is a congenital anomaly.

We will collect data on urgent care clinic visits, emergency department visits, and inpatient hospitalizations.

13.2 Reporting Procedures

The PI will be responsible for reporting unsolicited AEs to the IRB within 48 hours in iStar. The PI will follow-up by responding to questions as needed in iStar.

13.3 Follow-up for Adverse Events

Any AE will be analyzed for general risk to the entire cohort. In the event that an AE is generalizable to the entire cohort, all current study participants will be informed, and additional precautions will be developed and implemented. The PI will follow-up with the IRB responding to questions as needed to ensure the safety of participants until the issue is resolved or considered stable.

13.4 Safety Monitoring

- The study team will periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.
- Data reviewed: urgent care clinic visits, emergency department visits, and inpatient hospitalizations.
- The safety information will be collected (e.g., REDCap, at study visits).
- Frequency of data collection: during study visits, starting from baseline, weeks 4 and 8.
- The research team will review the data during biweekly meetings.
- As part of their training for the study, all personnel who will interact with subjects will receive instruction in identifying and reporting potential adverse reactions, including promptly reporting it to the PI (Dr. Larry Yin) and the research Co-Is and assistants.

14 STATISTICAL CONSIDERATIONS

14.1 Sample Size and Randomization

According to Julious (2005) a minimum sample size of 12 per group is needed for a randomized control pilot study. Accounting for 36% attrition, a minimum sample size of 34 adolescents is suggested to detect a medium effect size.

14.2 Treatment Assignment Procedures

After the adolescents meet all the eligibility criteria, they will be randomized by a random number generator to an intervention or a control group in REDCap. The research assistants will be responsible for maintaining the randomization list and ensuring that group assignments are implemented according to the protocol. Because this is an open-label study, participants and study staff will be aware of group assignment at the time of enrollment.

14.3 Interim Analyses and Stopping Rules

No interim analysis is planned, as this is a pilot study. Since this is a minimal risk study, we don't anticipate any safety findings or statistical rules that would temporarily suspend enrollment and/or study intervention. However, if there are any adverse events, we will follow IRB protocol until a safety review is convened (either routine or ad hoc) to determine whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed.

14.4 Outcomes

14.4.1 Primary outcome: Recruitment rate, retention rate, feasibility, usability, and acceptability.

14.4.2 Secondary outcomes: Inhaler proficiency technique score of device and observer rating score, FEV_1, and PEF measured at baseline, visit 2 (week 4), and visit 3 (week 8).

14.4.3 Tertiary outcomes: Adherence, satisfaction, and confidence

14.5 Data Analyses

Descriptive statistics will summarize participant demographics and baseline clinical outcomes overall and across groups: proportion (percentages) for categorical variables; mean (± standard deviation) for continuous variables; and median (interquartile range) for skewed or count

variables.

Aim 1: Feasibility will be assessed by recruitment rate, retention rate, number of days participants use their inhaler (adherence), and satisfaction. Descriptives statistics will be calculated to determine acceptability, usability, adherence, satisfaction, confidence, and motivation. Appropriate transformations will be used to generate approximately normally distributed variables when required by model assumptions. Linear mixed-effects models (LME/Multi-level) with a participant random effect will be fit to test the changes in each outcome between week 8 and baseline for each group. The model will include an interaction term visit*group to test whether the change is different between treatment and control. An identity link and normal family will be assumed for normally distributed outcomes. We will conduct both unadjusted and adjusted (for potential confounders such as age, race/ethnicity, and insurance) analyses. All results will be represented with model-based estimates, 95% confidence limits, and p-value of the corresponding hypothesis tests. Statistical significance will be defined using a two-sided $p < 0.05$.

We plan to add a stratification factor of gender to our randomization scheme to ensure balance between groups. We will conduct both unadjusted and adjusted (for potential confounders such as age, race/ethnicity, and insurance) analyses.

Aim 2: Outcomes of inhaler proficiency technique score, FEV_1, PEF and FeNO will be treated as continuous. Appropriate transformations will be used to generate approximately normally distributed variables when required by model assumptions. Linear mixed-effects models (LME/Multi-level) with a participant random effect will be fit to test the changes in each outcome between week 8 and baseline for each group. The model will include an interaction term visit*group to test whether the change is different between treatment and control. An identity link and normal family will be assumed for normally distributed outcomes. Establish effect size and the variability of the low effort changes the fractional concentration of exhaled nitric oxide, and effort dependent FEV_1 and PEF at week 8 from baseline between intervention and control groups. All results will be represented with model-based estimates, 95% confidence limits, and p-value of the corresponding hypothesis tests. Statistical significance will be defined using a two-sided $p < 0.05$.

Aim 3: Spearman's correlation test will be conducted to explore whether medication adherence and the deceive and observer inhaler technique score are associated with lung function.

We plan to add a stratification factor of gender to our randomization scheme to ensure balance between groups.

In accordance with NIH policy, a valid/exploratory analysis of the intervention effect will be performed in these subgroups: intervention effect between gender and racial/ethnic subgroups.

15 ETHICAL CONSIDERATIONS

Our ethical guidelines are derived from the Department of Health and Human Services (DHHS) final revision to the human subjects regulations known as the "Common Rule." These DHHS regulations are codified at Title 45 Part 46 of the Code of Federal Regulations. The revised regulations become effective on January 21, 2019, "The Revised Common Rule Compliance Dates and Transition Provision (45 CFR 46.101(l))". We will also follow the guiding ethical principles from the Declaration of Helsinki, CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or whichever provides the most protection to human subjects. We will also follow HIPAA (45 PARTS 160 AND 164). The HIPAA

Privacy Rule is under the jurisdiction of the Office of Civil Rights which is responsible for interpreting, establishing guidelines, and any subsequent modifications of the rule. Information regarding the most recent version of the Privacy Rule – Health Information Technology for Economic and Clinical Health (HITECH Act).

16 COMMITTEES

Publication Committee: Consists of PI and Co-Is who determine potential papers to publish.

17 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor prior to submission.

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