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|---|---|
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## TABLE OF CONTENTS

## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse event |
| API | Application Programming Interface |
| App | Mobile application |
| BTE | Bluetooth Low Energy |
| cACT | Child Asthma Control Test |
| CHOP | Children's Hospital of Philadelphia |
| CSV | Comma Separated Values |
| DHS | Department of Human Services |
| DMS | Data Management System |
| ED | Emergency Department |
| FDA | Food and Drug Administration |
| HAU | Healthcare Analytics Unit |
| ICS | Inhaled Corticosteroids |
| ID | Identification |
| PII | Personal Identifiable Information |
| PMACS | Penn Medicine Academic Computing Services |
| SAE | Serious Adverse Event |
| SQL | Structured Query Language |
| UPenn | University of Pennsylvania |
| WTH | Way to Health |

## ABSTRACT

Context: (Background)

Poor adherence to inhaled corticosteroid (ICS) medications for children with high risk asthma is a well-documented and poorly understood problem with a disproportionate prevalence and impact on urban minority children. Financial incentives have been shown as a compelling method to engage a high-risk asthma population in regular ICS use, but whether and how adherence can be maintained and lead to sustained high adherence trajectories is unknown.

Objectives: (primary and important secondary objectives)

1) Determine the marginal effects of financial ICS incentives on adherence (1° outcome) and healthcare system use and costs (2° outcomes) in a prospective cohort of child-caregiver dyads.
2) Assess proposed mechanisms by which intervention strategy influenced adherence trajectory, including (1) participant self-efficacy, (2) medication responsibility, and (3) habit formation.
3) Explore caregiver and child perceptions of acceptability of intervention components and how they influenced adherence trajectory.

Study Design:

Basic design: Randomized controlled trial

Setting/Participants:

To accomplish the above objectives, we propose to enroll 125 children and their parents in a six-month intervention with a six-month follow-up period. Children will be ages 5-12, and must have two or more visits to any combination of the outpatient, ED or hospital setting in the past year for asthma exacerbations at Children's Hospital of Philadelphia.

Study Interventions and Measures:

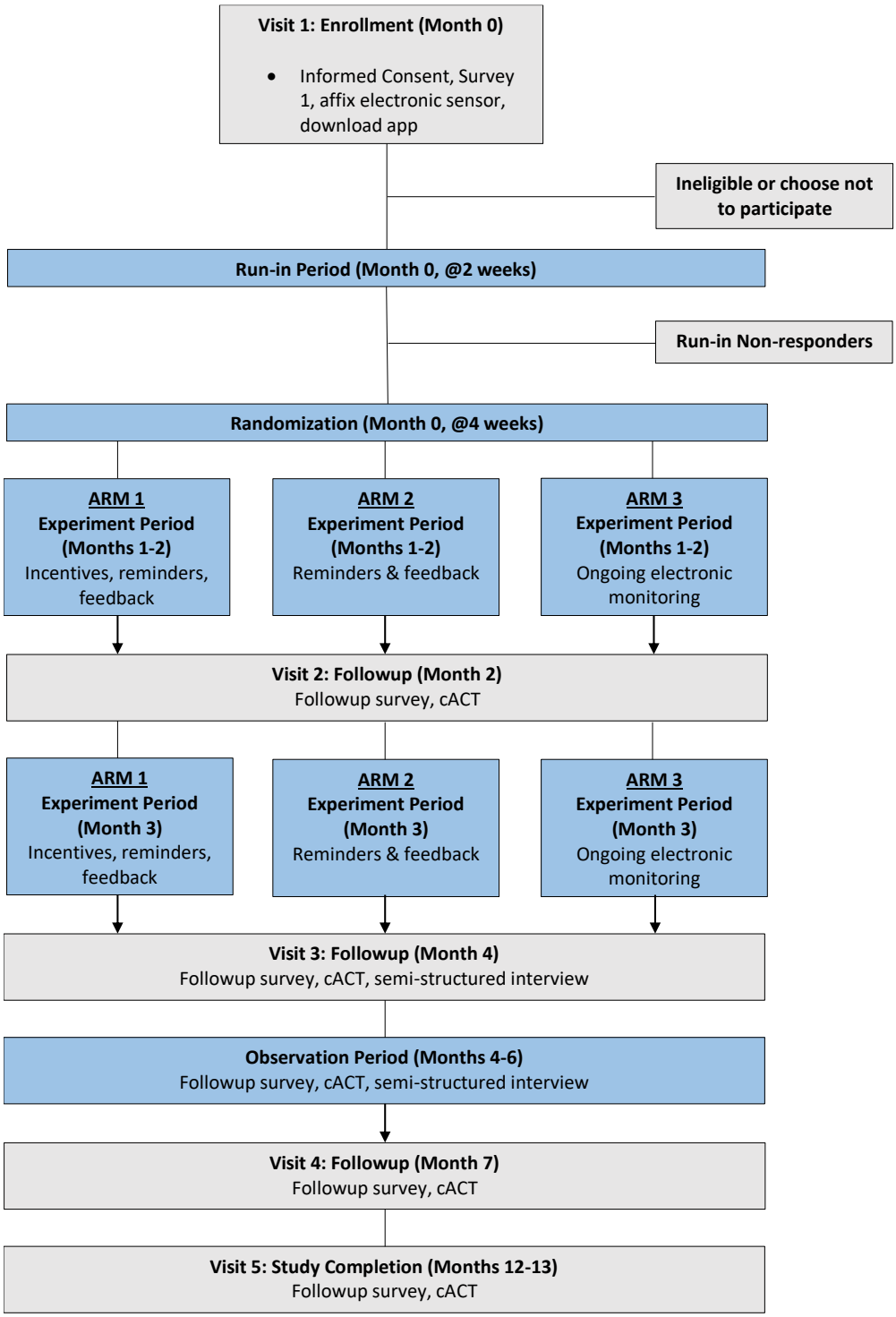
The study intervention will include daily automated medication reminders (either via text message or push reminder), an app to track daily medication use, and nominal incentives to promote daily controller use. Inhaled controller medication adherence and rescue medication use will be measured using electronic monitors affixed to the inhalers. Factors associated with differential adherence will be assessed using surveys administered during enrollment, the experiment interval (months 2 and 4), the observation interval (month 7), and study completion (months 12-13). Efficacy outcomes will include change in parent-reported asthma control and mean adherence to ICS between study arms during the experiment interval, as well as the observation interval.

## TABLE 1: SCHEDULE OF STUDY PROCEDURES

| **Study Phase** | **Screening and initial survey** | **Run-in period** | **Study survey** | **Experiment period** | | | **Study survey** | **Observation period** | **Study survey** | **Study completion survey** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1 (clinic /hospital/phone)** | | **2 (clinic/ phone)** | | | | **3 (clinic/ phone)** | | **4 (clinic/home phone)** | **5 (clinic/phone)** |
| **Arms** | **1,2,3** | **1,2,3** | **1,2,3** | **1** | **2** | **3** | **1,2,3** | **1,2,3** | **1,2,3** | **1,2,3** |
| **Study Month** | **0** | **0** | **2** | **1-3** | | | **4** | **4-6** | **7** | **12-13** |
| Informed Consent/Assent | X | | | | | | | | | |
| Review Inclusion/Exclusion Criteria | X | | | | | | | | | |
| Demographics/Medical History | X | | | | | | | | | |
| Prior/Concomitant Medications | X | | | | | | | | | |
| Dispense Electronic Monitors | X | | | | | | | | | |
| Questionnaires | X | | X | | | | X | | X | X |
| Child asthma control tool | X | | X | | | | X | | X | X |
| Electronic monitoring | | X | | X | X | X | | X | X | X |
| Daily medication reminders | | | | X | X | | | | | |
| Adherence incentives | | | | X | | | | | | |

## FIGURE 1: STUDY DIAGRAM

A flow diagram of the study is included below.



# 1 BACKGROUND INFORMATION AND RATIONALE

## 1.1 Introduction

Poor adherence to asthma controller medications is a well-documented yet poorly understood problem. Despite compelling evidence demonstrating improved disease control, fewer exacerbations, and hospitalizations with regular use of ICS, adherence with prescribed regimens for inhaled corticosteroids in childhood asthma is approximately 50% of prescribed doses.[1] In urban minority populations, who suffer higher rates of morbidity and mortality from asthma, adherence estimates are even lower, ranging from 11 to 37%.[2–5]

## 1.2 Name and Description of Investigational Product or Intervention

The intervention will be a three-arm randomized control trial that assesses the effects of different strategies for withdrawing financial incentives for ICS use targeting a cohort of children with multiple asthma hospitalizations in the preceding year. The intervention leverages mobile health technology to provide a daily cue (reminder message) and reward (feedback message with performance-based incentives) designed to reinforce routine ICS use.

## 1.3 Selection of Drugs and Dosages

No new medications will be prescribed as part of this intervention. We will use an FDA-registered Class 1 device that affixes to most common inhalers to assess the use of currently prescribed ICS and rescue medication during the study interval.

## 1.4 Relevant Literature and Data

Improving adherence, particularly in high-risk populations, is challenging. Previous interventions to improve medication adherence have demonstrated effects that are modest, at best[6,7]; thus, several emerging areas of study have catalyzed reinvestment in adherence interventions. First, technology-enhanced reminder systems have demonstrated robust ICS adherence improvements in other countries.[8–10] Second, adult interventions infused with financial and social incentives from behavioral economics have enhanced behaviors as varied as medication adherence to smoking cessation.[11,12] Few studies, however, have attempted to leverage mobile health technology and incentive design to improve medication adherence in children with high-risk asthma.

Two critical challenges limit the effectiveness of existing adherence interventions: (1) lack of knowledge of what it takes to engage high risk children and their caregivers, and (2) lack of enduring behavior change beyond the active intervention phase. Recent studies have begun to identify intervention components that tend to be more effective in engaging minority demographic groups[13] and lead to sustained behavior change or habit formation.[14] We recently conducted a pilot study of daily adherence reminders and feedback enriched with nominal financial adherence incentives ($1/day for 30 days for perfect adherence) in families of children ages 5-11 with 3 asthma hospitalizations in the prior year. Study enrollment (69%) and mean ICS adherence (80%) during the intervention month were robust; however, adherence dropped to 33% after incentives, reminders, and feedback ceased. These findings reveal that financial incentives are a compelling method to engage this high-risk asthma population in regular ICS use, but whether and how adherence can be maintained and lead to sustained high adherence trajectories is unknown in pediatric populations.

## 1.5 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

# 2 STUDY OBJECTIVES

The purpose of the study is to automate a technology intervention to determine ICS adherence trajectories in children who are at high risk for asthma hospitalizations, identify potential mechanisms for adherence, and assess the efficacy and acceptability of the intervention among children and caregivers.

## 2.1 Primary Objective (or Aim)

The primary objective of this study is to determine the marginal effects of financial ICS incentives on adherence (1° outcome) and healthcare system use and costs (2° outcomes) in a prospective cohort of child-caregiver dyads.

## 2.2 Secondary Objectives (or Aim)

The secondary objectives are to:

- Automate intervention delivery by developing a closed loop for electronic monitoring of ICS inhaler use and adherence incentive feedback.
- Assess proposed mechanisms by which intervention strategy influenced adherence trajectory, including (1) participant self-efficacy, (2) medication responsibility, and (3) habit formation.
- Explore caregiver and child perceptions of acceptability of intervention components and how they influenced adherence trajectory.

# 3 INVESTIGATIONAL PLAN

## 3.1 General Schema of Study Design

This is a three arm, randomized control trial study to assess the marginal effects of different strategies of financial incentives for ICS use targeting a cohort of children with high risk asthma.

### 3.1.1 Screening Phase

Potential subjects will be screened through the daily census listings for the inpatient units on the Epic medical record at CHOP using the protocol inclusion and exclusion criteria. Epic alerts and patient lists identifying high risk children with asthma will assist research staff in screening potential subjects.

Eligible children and their caregivers will be recruited during an asthma hospital admission, whenever possible, or in the month following hospital discharge, if the study team is unable to reach the family during the hospitalization. In the latter circumstance or if the child is eligible through asthma related outpatient visits, the study team will contact eligible participants by phone and if the caregiver expresses interest, the study team will approach the caregiver and child for informed consent/assent at a follow-up visit or via phone, if in-person recruitment is not feasible.

Parental/guardian permission (informed consent) and, if applicable, child assent, will be written on a physical copy of the consent form, when consent/enrollment takes place in person, prior to any study related procedures being performed. In the circumstance of telephonic enrollment, electronic consent via the REDCap platform will be obtained prior to any study related procedures.

If subjects consent to enrollment, the Study Run-in Phase will begin on the day of enrollment.

### 3.1.2 Run-in Phase (Month 0)

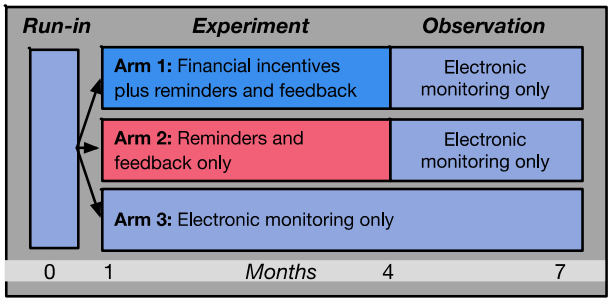



**Figure 2: Study schema for proposed RCT**

The study will be broken down into three discrete phases: (1) *Run-in* (2) *Experiment*, and (3) *Observation* (Figure 2). During the *Run-in* phase, every caregiver-child dyad will have access to the inhaler sensor app and will receive electronic ICS use monitoring. ICS use will be monitored using an electronic sensor that affixes to their ICS inhaler and will remain through the study *Observation* phase. Participants will be sent 4 text messages, each designed to elicit a response from the caregiver about the study technology or the study itself. (See Appendix 1 for content of the Run-in text messages) Participants for whom any inhaler use data is transmitted to the study platform within the first 2 weeks of the Run-in Phase AND reply to one or more of the 4 text messages sent from the study platform ("Responders") will be randomized into one of three arms at the end of the Run-in phase. (see section 4.10 for details on procedures for "Non-responders") The second two weeks of the Run-in Phase is designed to provide baseline adherence data.

### 3.1.3 Experiment Phase (Months 1-3) and Observation Phase (Months 4-6)

The three experimental conditions will be: financial incentives, adherence reminders, and feedback (Arm 1); adherence reminders and feedback without incentives (Arm 2); or electronic monitoring alone (Arm 3). The financial incentives in Arm 1 will consist of 3 months of fixed-ratio incentives for each ICS actuation (i.e. 25 cents per puff for children on 4 daily ICS doses and 50 cents per puff for children on 2 daily doses), with a maximum of $1 per day. With regard to the reminders and feedback in Arms 1 and 2, study participants will receive automated daily text message or push notification reminders and automated weekly feedback summarizing their adherence performance through Way to Health, a mobile health, electronic monitoring platform (described below in section 4.1). At the end of the first month of the experiment phase, families will be contacted by study staff to complete a follow-up survey that will reassess disease control, medication supply, and intentions and behaviors with

regard to ICS use (study visit 2). After the experiment interval, families will be contacted again by study staff to complete a follow-up survey and a semi-structured interview (study visit 3). At this point, all reminders, feedback, and incentives will cease, but daily ICS use monitoring will continue with the electronic sensors for all study arms (*Observation* phase) to assess for enduring effects. There will be a fourth study visit in the 7th study month, when study surveys will be completed, and a fifth and final study visit at one year assessing asthma control and health care utilization outside of the CHOP system.

For participants receiving adherence incentives in the experiment phase, accrued incentive value will be summed at the end of each 30-day interval (maximum $30) and added to a debit card that will be provided to the child upon enrollment. In the experiment phase, children randomized to Arms 2 and 3 who have any actuations recorded in the experiment phase will receive a $10 disbursement at the end of each month of the Experiment phase. Children in all 3 study arms will receive a $10 disbursement for each month during the Observation phase for which any adherence data (for the prior month) is transmitted to the platform. This compensation will not be contingent upon the participant's ICS adherence. Separate study visit compensation ($20) will be provided to the caregiver after enrollment and the 4th study visit, as well as after follow-up visits/calls at two, four, and 12-months.

#### 3.1.4 Follow-up Phase

After completion of the *Observation* interval, participants will enter into a follow-up phase. Participants will complete a brief final study survey at during months 12-13 with study staff. The study team will also assess the number of ED visits, hospitalizations, and oral steroid courses for asthma at CHOP over this time period within the CHOP EMR. Electronic monitoring of daily ICS medications will continue during the follow-up phase to assess for ongoing feasibility and acceptability of electronic monitoring, if the data is available.

### 3.2 Allocation to Treatment Groups and Blinding

Following consent, confirmation of eligibility, and the study Run-in phase (2-weeks to confirm that the participants' technology is functioning appropriately and 2-weeks to collect baseline data on the participants' adherence), patients will be assigned to one of three arms for the *Experiment* phase of the study using a 2:1:2 randomization scheme.

### 3.3 Study Duration, Enrollment and Number of Sites

#### 3.3.1 Duration of Study Participation

The study duration will be up to 13 months, beginning with screening and enrollment on day 1 and continuing through the study completion visit at the end of the follow-up period at 12-13 months.

#### 3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at CHOP alone.

We plan to enroll approximately 125 child-parent dyads. For our funder, enrollment will be reported as randomization into experiment phase.

## 3.4 Study Population

### 3.4.1 Inclusion Criteria

1) Males or females age 5 to 12 years and their parent or legal guardian.
2) Caregiver has an app enabled cellular phone (i.e., smartphone)
3) Prescribed inhaled corticosteroid or corticosteroid/long acting beta agonist combination for daily use
4) At least 2 asthma exacerbations in the preceding year (Any combination of hospitalizations, ED visits, or outpatient visits where oral steroid courses were administered for asthma)
5) Parental/guardian permission (informed consent) and if appropriate, child assent.

### 3.4.2 Exclusion Criteria

1) Subjects prescribed a controller medication to which the electronic device cannot affix: AirDuo (and generic AirDuo), QVAR Redihaler, Asmanex Twisthaler
2) Subjects in which the mobile app is not compatible with their smartphone model
3) Subjects with major developmental delays or disabilities
4) Subjects with comorbid chronic diagnoses that influence their asthma management such as cystic fibrosis, bronchopulmonary dysplasia, or cyanotic heart disease
5) Families with active Department of Human Services (DHS) involvement
6) Non-English speaking families
7) Parents/guardians or subjects whose medical team recommends against approaching for enrollment in a research study.

Subjects that do not meet all of the enrollment criteria will not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

# 4 STUDY PROCEDURES

## 4.1 Technology Integration

To automate the computation of daily ICS adherence incentives and feedback for our study, we will first create a closed data loop connecting ICS puff actuation data from the electronic inhaler sensor and mobile health app with the Way to Health (WTH) platform. WTH is an NIH-sponsored, web-based platform that automates many of the research functions necessary for conducting randomized controlled trials of behavioral incentives. It has been used in numerous prior research studies.[15–17] We will obtain the application programming interface (API) of the electronic inhaler actuation sensor (developed by Propeller Health, a sensor company with whom we have worked previously). We will work with WTH staff to program the computation of ICS adherence incentives and language of weekly adherence feedback messages to study participants. This integrated infrastructure will facilitate transmission of daily adherence data from the inhaler sensor platform to Way to Health via the sensor API.

Way to Health will use the adherence data to automatically tabulate financial incentives and send weekly adherence feedback messages to participants. We will collaborate with the engineering teams at WTH and Propeller to develop this integrated infrastructure. The WTH team has previously integrated 11 devices similar to this sensor for prior research studies.

## 4.2 Screening Visit (Visit 1)

- Note: For some participants Visit 1 may be completed in the hospital or at a follow-up visit in the month following hospitalization. This will be done 1) to accommodate participants' preferences and scheduling, and 2) to ensure that electronic monitors are provided when the child's asthma control inhaler is available for the device to be attached. For participants enrolled after physical distancing measures set in place for COVID-19, Visit 1 may be completed over the phone. This will be done 1) to ensure the safety of participants and study personnel, and 2) in accordance with hospital policy preventing study personnel from approaching patients in the hospital. In this circumstance, electronic monitoring devices will mailed to participants following telephonic enrollment.

- Informed Consent

- Epic Medical Record Review

- Study visit 1 survey question blocks (see section 4.11.2)

- Dispense and explain use of electronic monitoring devices

- Download and set up inhaler sensor app

## 4.3 Study Run-in Phase (Phase 1)

The study run-in phase will begin once families complete the screening visit. A study team member will instruct the family to use the inhaler as directed by their physicians and to care for the child's asthma as directed by the child's physicians.

Data collected during the study visits will be stored on the secure WTH web-based platform. Adherence monitoring data will be stored on the secure Propeller Health web-based platform and downloaded to WTH in real-time through the integrated API (see Section 7.2: Data Collection and Management for full descriptions of the WTH and sensor platforms, as well as the data management plan details).

## 4.4 Study Experiment Phase (Phase 2)

The child-caregiver dyads will be randomized into one of three arms for months 1-3: (1) receiving daily reminders, weekly feedback, and incentives, (2) receiving reminders and weekly feedback without incentives, or (3) receiving no reminders, feedback, or incentives. Participants will not know which group they are randomized to until they begin this phase of the study. Study participants will be contacted by telephone call or text message to inform them to which study arm they were randomized. At this time, study staff will help participants randomized to Arm 1 select an adherence reward goal of $30 value.

## 4.5 Visit 2 (clinic or home preferred, telephone if not possible) – month 2

- Study visit 2 survey question blocks (see section 4.11.2)
- Equipment and medication refill check

## 4.6 Visit 3 (clinic or home preferred, telephone if not possible) – month 4

- Study visit 3 survey question blocks (see section 4.11.2)
- Semi-structured interview on intervention experiences and preferences
- Equipment and medication refill check

## 4.7 Study Observation Phase (Phase 3)

During months 4-6, all three arms will be in the observation phase, in which none of the participants receive reminders, feedback, or adherence-contingent incentives.

## 4.8 Visit 4 (clinic or home preferred, telephone if not possible) – month 7

- Study visit 4 survey question blocks (see section 4.11.2)

## 4.9 Visit 5 (clinic or telephone) – month 12-13

- Study visit 5 survey question blocks (see section 4.11.2)

## 4.10 Subject Completion/Withdrawal

Because the study intervention is dependent on functioning cellphone-sensor-platform data connection, subjects for whom the research staff cannot establish a functional adherence data feed and two-way text message communication with-in two weeks of enrollment will not be randomized by study staff. Specifically, these "non-responders", for whom no electronic adherence data is transmitted and do not reply to any of the 4 text messages sent during the first two weeks of the Run-in Phase, will not undergo randomization and enter into the Experiment or Observation Phases. This criteria for randomization will be explicitly stated in the study informed consent form. Participants will be informed that their data from the Electronic Health Record can still be accessed and used as part of this research and data collection until the study ends. In order to take back this permission, participants must inform the study team of their wish to withdraw from the study.

Additionally, subjects may withdraw from the study at any time. They may also be discontinued from the study at the discretion of the Principal Investigator for inappropriate or threatening behavior with study staff.

### 4.10.1 Early Termination Study Visit

Subjects who withdraw from the study will have all procedures enumerated for Visit 1, 2, 3 or 4 as the early termination visit. Participants who withdraw from the study prior to completion will have the option to have their earlier responses redacted from the database. If

participants choose this option, any data collected in study visits 1-4 will be excluded from subsequent analysis.

## 4.11 Screening and Monitoring Evaluations and Measurements

### 4.11.1 Medical Record Review

Variables to be abstracted from the medical chart:

- Child sex
- Date of birth
- Weight and height
- Date of qualifying hospital admission and discharge
- Asthma severity
- Last spirometry result and date of assessment (if reported)
- Name and dose of current asthma medications (both controllers and rescue)
- Number of prescriptions and refills in the prior year for each asthma medication
- Number and date of ED visits, hospitalizations, and oral steroid courses for asthma in the preceding year
- Number and date of ED visits, hospitalizations, and oral steroid courses for asthma during the 13-month study period

### 4.11.2 Other Evaluations, Measures

The following instruments (or question blocks from the following instruments) will be used to assess key constructs at each study visit:

- Child and parent self-efficacy, measured using the Child and Parent Asthma Management Self Efficacy scale[18],
- Parent/child responsibility for asthma care measured using the Asthma Responsibility Questionnaire[19],
- ICS habit strength, measured using the Habit Strength Index adapted for asthma controller use[20].

## 4.12 Efficacy Evaluations

We will collect a number of efficacy outcomes including parent reported asthma control and use of prescribed medicine over the study interval.

### 4.12.1 Diagnostic Tests, Scales, Measures, etc.

- Child Asthma Control Tool (cACT)
- Daily Medication adherence – calculated as the mean daily proportion of prescribed doses taken by study month. Days that reflect >1 will be truncated to 1.

## 4.13 Safety Evaluation

Subject safety will be monitored by adverse events.

## 4.14 Primary Endpoint

The primary outcome will be adherence to ICS regimen both during the *Experiment* interval (months 1-3). Adherence over these study intervals will be characterized as a daily observed-to-prescribed ICS adherence proportion averaged by study month. To operationalize this, a daily medication use log composed of 180 sequential ICS use observations will be generated, representing the count of ICS doses taken each day of study enrollment. These daily counts will be converted into proportions by dividing by the daily prescribed dose and imposing an upper limit of 1 in order to prevent doses taken above the prescribed limit – either during the use of flare plans or attempted "gaming" of the incentives by the participants – from influencing interval adherence estimates. Observed actuations will be quantified using electronic sensors.

## 4.15 Secondary Endpoints

Secondary endpoints will include the following:

- Adherence to ICS regimen in *Observation* interval (months 4-6)
- Adherence trajectory, as determined by group-based modeling of adherence patterns.
- Change in cACT score from first study visit to the second, third, fourth, and fifth study visits.
- Number of asthma-related emergency room visits, hospitalizations, and oral steroid courses between study conditions.
- Healthcare costs associated with emergency room visits, hospitalizations, and oral steroid courses between study conditions.
- Continued use of sensors in 7-13 month follow-up period (feasibility outcome)

Health system use outcomes will be assessed primarily using CHOP electronic health record data and, secondarily, via caregiver report to account for utilization that may have occurred outside of CHOP. ED visits, hospitalizations, and oral steroids courses will be characterized as asthma-specific using existing, validated asthma registry definitions that include asthma visit diagnoses, medication orders, and asthma pathway order set activation. Costs will be estimated using average insurance payments for asthma ED visits, hospitalizations, and oral steroid courses in addition to the costs of the intervention components (i.e. sensors, incentive value, and research staff support).

## 4.16 Statistical Methods

### 4.16.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

### 4.16.2 Efficacy Analysis

We will assess the effectiveness of randomization by comparing the study arm balance on key demographic, clinical, and past health care utilization variables using analysis of variance (ANOVA) and t-tests or the nonparametric equivalent for continuous variables and chi-square tests or Fisher exact tests for categorical variables.

*Primary analysis:* Our primary outcome will be monthly ICS adherence in months 0-3 (Experiment Phase). Secondary outcomes will include monthly ICS adherence in months 4-6 (Observation Phase), asthma control at the end of the Experiment and Observation period. Secondary outcomes will also include monthly ICS adherence in months 7-13 (follow up period) to assess feasibility and acceptability of longer durations of electronic monitoring. We will consider arcsine transformation on the ICS adherence outcomes as necessary. This technique is commonly used for proportion data. We will use generalized estimating equations (GEE) to adjust for within-subject correlations due to repeated measures for the study's primary and secondary monthly adherence outcomes. Models will include main effects for arm and time (month) and arm-by-month interaction terms to allow for differing ICS adherence over time between arms. The dependent variable of monthly ICS adherence will be defined as mean daily observed-to-prescribed ICS actuation proportion for each study month. Mean daily adherence proportion will be capped at 1, such that participants taking more than their prescribed daily dose cannot receive "extra credit" for doses taken on those days. All statistical tests will be 2-sided. A P-value <0.05 will be considered statistically significant.

*Secondary analysis:* We will construct adherence trajectories for the combined *Experiment* + *Observation* interval for each study participant using group based trajectory modeling (GBTM). This modeling approach accounts for changing behavior over time and allows for identification of several distinctive developmental progressions without imposing the requirement that they vary normally about the population mean.[21,22] Thus, participants with similar daily adherence trajectories are grouped about similar longitudinal trends and the model output is probabilistic assignment of each individual to one of several (up to six) adherence groups. Based on group-based modeling research on medication adherence from other conditions, anticipated ICS trajectory groupings will likely include: (1) severe early non-adherence, (2) severe delayed non-adherence, (3) moderate or episodic non-adherence, and (4) sustained adherence.[23,24] (See Figure 3 for a preliminary 3-group ICS adherence trajectory model from our prior work.) Adherence group/category will then become the dependent variable for subsequent analysis in which a multinomial or ordered logistic regression will be applied with treatment arm as the exposure, adjusting for the covariates

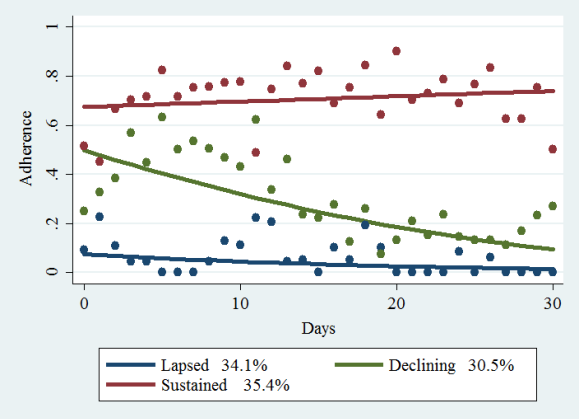



**Figure 3:** 30-day post-discharge ICS adherence trajectories. (From Kenyon, et al. *J Asthma*. 2018.)

described above. For each adherence trajectory group, relative risk ratios for arms 1 and 2 compared to arm 3 will be calculated. We will test for overall effect of treatment arm on adherence trajectory in addition to important permutations (i.e. Arm 1 compared to Arm 3 within sustained adherence trajectory) using chi-square tests and generate marginal estimates of the probability of trajectory group membership, given treatment arm assignment (e.g. the probability of being in the sustained trajectory group if randomized to Arm 1 vs Arm 2 vs Arm 3). Findings presented alongside the primary analysis of observed-to-prescribed interval adherence percentage.

## 4.17 Sample Size and Power

Our analysis of pilot data demonstrates a 48% difference in ICS adherence when comparing a time interval with financial incentives (the same schema proposed in this study) to a time period without incentives. To ensure a power of 80% at a significance level of 0.05 to detect a more conservative 30% difference in average adherence between arms 1 and 3 in the *Experiment* phase (corresponding to 65% and 35%, respectively), 40 patients are required in each of these two arms. To ensure scientific rigor given the vulnerable nature of the population, we estimate ~20% loss to follow-up. Therefore, we will aim to enroll 50 participants in study arms 1 and 3 and 25 participants in arm 2, or 125 participants total, to achieve sufficient power to detect a difference between arms 1 and 3. The study is not to be powered to detect differences in arms 1 to 2 or 2 to 3 (hence the 2:1:2 randomization schema) or for health outcomes or cost offset; rather, it is intended to obtain preliminary estimates of marginal effects of the intervention components and effect sizes on utilization outcomes by comparing arm 1 to 2 and 2 to 3 to power a future multicenter study. Baseline data reveals that ~50% of children with at least 2 prior hospitalizations have a repeat ED visit or inpatient stay 6 months after the 2$^{nd}$ hospital discharge.

## 4.18 Additional analyses

*Hypothesis 1.2* Longer time intervals to next asthma-related ED or inpatient visit, and reduced healthcare use and costs, will be observed in Arm 1 compared to Arms 2 and 3 (and in Arm 2 compared to Arm 3).

Time to next asthma-related ED or inpatient visit from enrollment will be first modeled using the Kaplan-Meier plots. Study arms will be compared using log-rank tests and unadjusted Cox proportion hazards models. Adjusted hazard models will include the additional covariates described above and the Anderson-Gill method will be used to account for recurrent events. Total medical costs will be estimated for the 12 months following study enrollment, accounting for each asthma-related ED visit and hospitalization, as well as the expenses incurred with study participant incentives, sensors, and use of the WTH automated platform. We predict that intervention will reduce medical costs, thereby contributing to a *cost offset*. We will estimate potential savings in medical costs by calculating the difference in average total medical costs minus study-related expenses between study arms.

**<u>Aim 2.</u> Assess proposed mechanisms by which intervention strategy influenced adherence trajectory.**

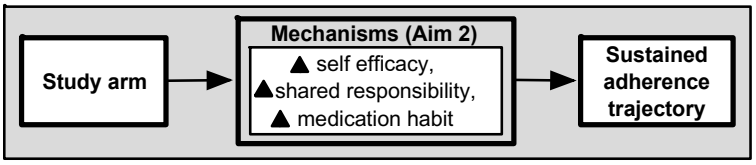



**Figure 4:** Potential mechanisms for study arm effect on adherence trajectory

<u>Aim overview:</u> The broad goal of this aim is to assess which participant and study characteristics are associated with different longitudinal adherence trajectories. Characteristics to be examined include baseline factors (demographic, clinical, and prior health utilization factors), intervention strategy (study arm), and potentially modifiable behavioral characteristics. Of specific interest is how intervention strategy in the Experiment phase (study arm) influences child asthma self-efficacy, shared medication responsibility, and medication habit over time and how these characteristics vary with longitudinal ICS adherence trajectories. **[Figure 4]**

*Hypothesis 2:* Increases in (1) participant self-efficacy, (2) shared medication responsibility, and (3) habit score will partially mediate the relationship between study arm and sustained adherence trajectory.

ICS adherence trajectories will be characterized using group-based trajectory modeling (GBTM). GBTM is an analytic technique used to identify and characterize differential patterns of changing behavior over time in a population of interest. In GBTM, an individual is assumed to belong to only one group, of which each group has its own trajectory. I will specify several models with different number of groups (e.g. 2 to 5) using quadratic trajectories (or possibly higher order polynomials) and compare these models to identify the one that best fits our ICS use data based on both the Bayesian information criterion and group percentages that are sufficiently large (e.g. >5% of the entire sample) to ensure study power as well as model stability. The group-based trajectory modeling will be performed using PROC TRAJ macro implemented in SAS (SAS 9.3).

Once adherence trajectory groups have been determined, I will first use bivariate multinomial or ordered logistic regression models to estimate odds ratios (ORs) for the three predictors of interest, as well as baseline demographic, clinical, and health utilization characteristics, on trajectory group membership. When applying the ordered logistic regression, I will check the proportional odds assumption using the Brant test. All variables that are not marginally predictive of any trajectory group in bivariate analyses (P-value>0.2) will not be included in the multivariable analysis. I will then construct a final multivariable multinomial regression model of trajectory of all marginally predictive covariates, first including (1) baseline demographic and clinical characteristics, then (2) study arm, and lastly, (3) the three hypothesized potential mechanisms.[7] Mediation analysis will be conducted with variables associated with both study arm and trajectory membership. Covariance matrices will be generated and regression estimates standardized to obtain an overall mediated effect of each potential mechanism variable (e.g. child self-efficacy) on each study arm. The percentage of the total effect of study arm that is mediated by child self-efficacy, for instance, will be calculated using standardized beta estimates.[8] If self-efficacy, shared responsibility, and habit index are not associated with study arm or adherence trajectory, I will then assess the additional behavioral constructs described in the "Covariates" section (medication beliefs,

descriptive and injunctive norms, and current asthma symptom burden) as potential alternative mediators.

**Aim 3. Explore caregiver and child perceptions of acceptability of intervention components and how they influenced adherence trajectory.**

Aim overview: The final aim will use data from the semi-structured interviews conducted at the 6-month visit in a randomly selected subset of study participants to gain in-depth insight into the family and child experience of the intervention components with particular attention to perceived influence, or lack of influence, of the ICS adherence incentives on adherence behavior. In addition, we will explore other factors children and caregivers perceived as influencing their daily ICS adherence. Interview prompts will include the perceived impact of the intervention components (financial incentives, adherence reminders, adherence feedback, study app, electronic monitoring), component design factors (duration of incentive exposure, duration and frequency of reminders and feedback, child and caregiver engagement strategies, and potential alternative incentive strategies), and non-intervention factors (medication access, perceived medication efficacy, and family and social circumstances). Using the trajectory groupings derived from the prior aims, we will then assess whether themes differ between families of children with different daily use trajectories.

Semi-structured interviews will be audio-recorded. Audio files will be transcribed verbatim. Field notes and interview transcripts will be uploaded to NVivo 12 software. Co-mentor Dr. Victoria Miller will help train a research assistant to assist in the coding of data. We will use inductive theory-building[9] and the constant comparative method[10] to identify data patterns. We will first read through all documents using open coding to record salient themes that emerge that will be further refined during axial coding in a second stage. At this stage, we will begin to generate explanations for emerging patterns in the data. After generating a draft code list, we will review interview transcripts and our field notes to determine which codes fit the concepts suggested by the data. As we discover themes and patterns, we will consistently search for negative cases within the data to refine our analysis.[11] Coding discrepancies will be logged and discussed by myself, co-mentor Dr. Miller, and the research assistant to examine reasons for the discrepancy, to inform theory and interpretation of the data, and refine analytic procedures.

We will then use trajectory group membership from the prior aims to categorize participants into sustained ICS versus non-sustained trajectory and explore the ways in which perceived intervention effects and experiences differ between these groups. If the distribution allows, we will attempt further categorization of the non-sustained group into specific trajectory grouping (i.e. severe early non-adherence, intermittent adherence, etc).

# 5 STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

## 5.1 Description

There is no study medication or device that is being evaluated in this study. Rather, the reminder, feedback, and incentive intervention described above will be the subject of investigation. In order to capture ICS medication use, we will use an electronic sensor device (described below) that attaches to the exterior of the ICS inhaler and transmits pressure-activated device actuation data via Bluetooth to a mobile phone app. The Propeller sensors (Propeller, Madison, Wisconsin) are FDA 510k cleared, portable device attaches onto a patient's asthma medication (see exclusion criteria in section 3.4.2 for a list of medications that are not compatible with the Propeller sensor). These devices record the time and date of each inhaler actuation and transmit this information via Bluetooth to either a smartphone or hub. Data is then sent via the cellular network to the secure Propeller server. The data will then be transmitted onto the secure, password-protected Way to Health platform through the integrated API.

# 6 SAFETY MANAGEMENT

## 6.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study. However, since this is a minimal risk study, we do not expect clinical adverse events to be related to study procedures.

## 6.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. SAE and AE reporting are summarized in the DSMP in Appendix 2.

# 7 STUDY ADMINISTRATION

## 7.1 Treatment Assignment Methods

### 7.1.1 Randomization

At the time of enrollment, patients will be assigned to one of three arms using a 2:1:2 block randomization scheme with a block size of 50. Randomization will be accomplished automatically by the Way to Health web-based platform. During the Run-in interval of the study, every caregiver-child dyad will receive electronic ICS use monitoring. Participants for whom we received any adherence monitoring data and at least one text message reply by the end of week 2 will be randomized into one of three experimental conditions at the end of the Run-in period.

Participants will be randomized using block randomization, so arms 1 and 3 will have approximately equal sample sizes and arm 2 will have approximately half the number of

participants(as the study is powered to detect a difference between arms 1 and 3). A total n of 125 will be randomized, with a recruitment goal of about 50 in arms 1 and 3 and 25 in arm 2.

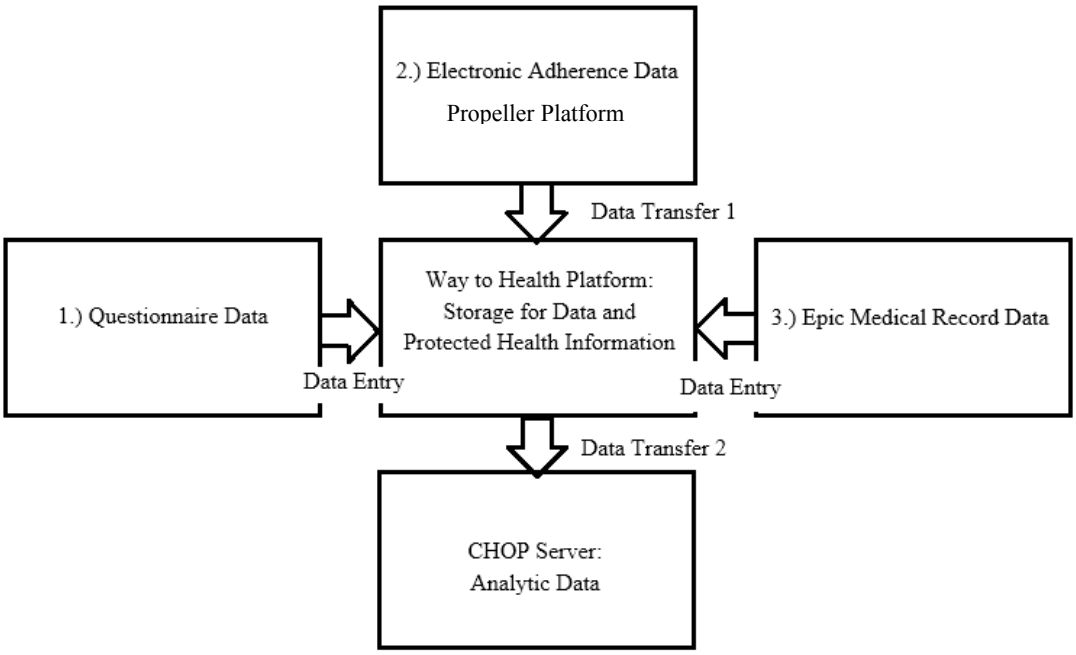
### 7.1.2 Blinding

Only the PI (Dr. Kenyon) and the statistics team will remain blinded to the assignment of study arm. Neither the subjects nor the study team will be blinded to the study conditions, given that the intervention groups will be receiving incentives and/or reminders (whereas the control group will not) and the study team will provide monthly incentive payments and help facilitate tech support based on the study arm.

## 7.2 Data Collection and Management

Each study subject will be assigned a study ID at the time of enrollment, which will serve as the means of protecting personal health information during data transfers and storage. These master study IDs will be kept in a separate CHOP network folder from the datasets and will be retained for at least 6 years according to CHOP policy A-3-9.

Epic medical record and study questionnaire data will be entered directly into the Way to Health platform (in the case of patient identifiable information) or on a paper form during the study visits. Coded electronic adherence data will be transferred electronically from the Propeller Health Platform to the Way to Health Platform via the API of the Propeller sensor. An additional data transfer will be used to extract a coded analytic data set to the secure CHOP research server for analysis. All databases created will be password-protected and only study team members will have access. All data sets downloaded through the Propeller Health or Way to Health platforms will be password-protected and stored on the CHOP secured network drive, only accessible to study team members. For a summary of data entry and transfer, refer to Figure 4 below.




Way to Health Platform:

Research material will be obtained from participant surveys entered directly into the Way to Health portal, and from the data transmitted from Propeller Health's device trackers to the WTH platform via the integrated API. Research material that is obtained will be used for research purposes only. The same procedure used for the analysis of automated data sources to ensure protection of patient information will be used for the survey data, in that patient identifiers will be used only for linkage purposes or to contact patients. The study identification number, and not other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project and is where the Way to Health web portal is based. The PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. The PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. Among the IT projects currently managed by PMACS are: (1) the capture and organization of complex, longitudinal clinical data via web and clinical applications portals from cancer patients enrolled in clinical trials; (2) the integration of genetic array databases and clinical data obtained from patients with cardiovascular disease; (3) computational biology and cytometry database management and analyses; (4) economic and health policy research using Medicare claims from over 40 million Medicare beneficiaries. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations. All data for this project will be stored on the secure/firewalled servers of the PMACS Data Center, in data files that will be protected by multiple password layers. These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by University of Pennsylvania system managers. We will use highly secure methods of data encryption for all transactions involving participants' financial information using a level of security comparable to what is used in commercial financial transactions. We believe this multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health Systems medical records, greatly minimizes the risk of loss of privacy. In addition, risk of loss of confidentiality will be minimized by immediately destroying paper copies of surveys after entering data into the WTH platform. Each subject will be assigned a unique identifier without identifying information, and data will be entered into an electronic database using only the unique identifier. Only trained study staff will have access to the code that links the unique identifier to the subject's identity. Electronic data will be stored on secure, password-protected firewalled servers at the University of Pennsylvania and Children's Hospital of Philadelphia.

WTH uses a role-based access control (RBAC) approach to assure that participant confidentially and study integrity is preserved. Principle investigators and statisticians are

restricted using RBAC, with a role that provides them access to coded data sets only. Other staff such as project managers and research coordinators require access to identifiable data in order to conduct normal study operations such as follow up study visits, monitoring enrollment statuses, and updating contact information. These roles can toggle between identified and coded views as needed. Prior to receiving access to the platform, the study's project manager must confirm that the staff person has been added to the IRB and has completed their CITI Protection of Human Subjects Research Training – ORA. Research staff users must read and sign the WTH Data Security Agreement upon initial login to the platform. They cannot access PHI or any other data on the platform until that agreement has been reviewed and signed.

The WTH Team supports all research studies run on the platform. Default views within the platform for all WTH staff display coded participant data. As a part of support and troubleshooting, the WTH Team is trained to use only these coded views. In rare cases where the issue involves viewing identifiable participant data, the WTH team may need to view this data to assist the study team.

The WTH Team are employees of the University of Pennsylvania and Penn Medicine. All WTH team members have completed HIPAA Security training and CITI Protection of Human Subjects Research Training - ORA.

Access to the backend database is restricted and only available to a select group of developers. The database is accessible only via a secure VPN (Virtual Private Network) and cannot be accessed from the public internet at all, i.e. authorized users can only access the databases from within Penn's network and over a secure VPN channel.

To maximize security, WTH assumes that **all** data in the system is electronic protected health information (ePHI). All data at-rest is stored on encrypted disks using encryption keys managed by WTH. Encrypted disks use AES encryption with a minimum of 256-bit keys, or keys and ciphers of equivalent or higher cryptographic strength. User passwords are never stored in clear text; they are "salted" and "hashed" to eliminate data leakage. All data transmission is encrypted end to end using encryption keys managed by WTH. Transmission encryption keys use a minimum of 2048-bit RSA keys, or keys and ciphers of equivalent or higher cryptographic strength (e.g., 256-bit AES session keys in the case of IPsec encryption). Data downloads are generally prohibited by policy. Where appropriate, most datasets are blinded of all personally identifiable information when exported for analysis. A limited number of exports including identifiers exist to assist research staff with recruitment tracking and study management efforts. These datasets are only accessible to certain user roles. These user roles are required to sign and adhere to a WTH Security Agreement as described above

To monitor ongoing usage of the system and identify unauthorized usage of the system, all access to the application and the database are logged automatically. These logs are reviewed as described in the WTH policies.

WTH has automated procedures to create and maintain retrievable exact copies of ePHI utilizing our Backup Service. These backup procedures are run on a daily basis and stored in a different location. Backups are encrypted. Backups are retained for a rolling 14 day period. Recovery from backups is also tested on a quarterly basis.

Security is a paramount concern at WTH. We perform regular (at least monthly) vulnerability scans of our systems to identify and patch any known vulnerabilities in our systems. We also run Intrusion Detection Systems (IDS) to identify unauthorized system access.

1) Questionnaire Data:

This study will use *Way to Health's* online survey tool to collect answers to survey questions from participants. Survey answers will be entered by the study team member and are stored on the *Way to Health* platform. Study staff members review the survey content to ensure that no questions in any of the surveys ask for patient identifiers. If there are problems connecting to the internet for questions to be completed on a laptop computer, a paper form of the WTH surveys will be used. All paper surveys will be recorded in WTH at the earliest possible convenience by study staff. Paper forms will be inserted into a locked box for materials to be shredded once information is entered and confirmed into WTH.

2) Electronic Adherence Data (Propeller Health sensor and platform):

Following activation of the electronic monitoring device, time-stamped data is transferred from the electronic monitoring device via Bluetooth to a smartphone or cellular modem, which then sends it via the cellular network to the Propeller platform. The cellular upload identifies the patient only by a unique identifier. The cellular transmission has no patient-identifying information and no IP addresses are collected during this information transfer. The coded daily adherence data will then be available to the study team on the secure, password-protected Propeller provider platform.

Data collected in Propeller are stored within a US HIPAA compliant system, meaning that personal health information is protected during capture, during transmission to the server, and when on the server. Propeller has been certified to offer industry leading policies and controls for data protection under the HITRUST framework. For more information, anyone (including patients and providers) can visit https://www.propellerhealth.com/privacy-policy/

**Propeller HIPAA Adherence statement:**

Data collected in Propeller are stored within a US HIPAA compliant system, meaning that personal health information is protected during capture, during transmission to the server, and when on the server. Propeller has been certified to offer industry leading policies and controls for data protection under the HITRUST framework. For more information, anyone (including patients and providers) can visit https://www.propellerhealth.com/privacy-policy/

3) Epic Medical Record Data:

Study staff will extract asthma-related primary care, ED, and hospital data points (see Section 4.11.1 for specific data points to be extracted) from Epic into Way to Health via individual chart review. Individual patient data will be labeled with the patient's study ID upon population of Way to Health for subsequent storage and data analysis.

4) Semi-structured interviews:

Semi-structured interviews will be recorded via two-way microphones. Recordings will be uploaded to a secure site for transcription (by ADA transcription service; agreement in place for this study). Then transcripts will be downloaded to our secure CHOP network drive and uploaded into NVivo, a qualitative software program that meets CHOP's IT standards for security, for coding and analysis.

Data Transfer Description

1.) Propeller platform to Way to Health platform: coded study adherence data will be transferred from Propeller Health to the Way to Health platform through the integrated API. This file will contain no PHI, only the subjects' study ID. Way to Health will use the adherence data to automatically tabulate financial incentives and send weekly adherence feedback messages to participants.

2.) Way to Health to CHOP Server: Coded data from the study visits, including initial survey, follow-up surveys, and electronic adherence data will be converted to a CSV file and uploaded onto the CHOP server to a dedicated research folder on the study PI's virtual desktop. No PHI will be involved in this transfer, only the subject's study ID.

The Health Analytics Unit (HAU) will assist the study staff in converting these coded data from the CSV file to an analytic file for subsequent cleaning and analysis. All transferred and created files will be stored in a password-protected folder available only to study staff on CHOP's secured shared network drive. The study key will be stored in a separate password protected folder assigned to this study. All identifiers will be deleted following publication of the study results.

Study Recruitment Tracking File:

Recruitment and enrollment tracking will be stored in a REDCap database, only available to study team members. This database will include patient identifying information necessary for registration, enrollment, and follow-up (see 9.6, waiver of HIPAA authorization). Following enrollment, this database will be used to maintain a log of enrolled patients. For families who are not enrolled, patient identifying information will be destroyed. A non-identifiable list of patients that were not enrolled will be retained for the purpose of calculating response rate.

Consent Forms:

Consent will be obtained using a physical copy of the form if enrollment is conducted in person. REDCap electronic consent will be obtained if initial enrollment is conducted via telephone. Families will receive an electronic copy of the consent form that they will digitally sign. If consent is not obtained electronically, paper consent forms will be stored in a locked filing cabinet and retained per CHOP policy A-3-9.

Anonymization:

Data will be extracted from the secure WTH platform for the purpose of data analysis. Any datasets and computer files that leave the WTH firewall will be stripped of all identifiers and individuals will be referred to by their study ID. The study ID will also be used on all analytical files.

## 7.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

Survey and interview responses will be stored on the WTH platform. The site is HIPAA compliant. Please see Section 9.2 for measures taken to assure confidentiality.

Data regarding adherence to metered-dose inhaler use will be stored on the website of Propeller Health and transferred to the WTH platform through the integrated API. The Propeller Health site is HIPAA compliant. Please see Section 7.2 for measures taken to assure confidentiality.

No identifiable data will be used for future study without first obtaining IRB approval.

## 7.4 Regulatory and Ethical Considerations

### 7.4.1 Data and Safety Monitoring Plan

Please see Appendix 2 for the DSMP for this study. A local DSMB has been appointed for this study with guidance from the Clinical Trials Office at the NHLBI. The PI has developed a number of additional strategies to ensure the accuracy, security, and validity of the various data sources. First, identifiable information will be converted to study ID for storage and analysis. Data extracted from the Epic medical record by the research assistant and the study questionnaire responses will be entered into and stored in the WTH platform at Penn by study ID. Coded adherence data from the Propeller platform will be downloaded to the WTH platform in data downloads through the API.

Second, the data sources that will contain identifiable information, namely the Propeller and WTH platforms, will be held to the highest of security standards. Please see section 7.2 for the security features of the Propeller and WTH platforms.

Please see section 7.2 for further details of the measures in place to protect data confidentiality, especially with respect to data transfers.

### 7.4.2 Risk Assessment

Risks are minimal. There is no risk or discomfort to the study intervention. The study intervention merely adds electronic monitoring and text message notifications to already prescribed medications. The main risk is breach of confidentiality. Please refer to the above Sections 7.2, 7.3, and 7.4.1 for a list of strategies in place to avoid a breach of confidentiality.

### 7.4.3 Potential Benefits of Trial Participation

Improving adherence may lead to better control of asthma and therefore decrease school absences, parental work absences, and the number of visits to the ED or admissions to the hospitals.

### 7.4.4 Risk-Benefit Assessment

The risks of this study are minimal. The main risk of the study is breach of confidentiality. Methods of avoiding a potential breach of confidentiality are described above in Sections 7.2, 7.3, and 7.4.1. The potential to improve asthma adherence may improve asthma control and

decrease ED visits or hospital admissions for asthma. The potential benefits of study participation outweigh the risks.

## 7.5 Recruitment Strategy

### 7.5.1 Recruitment Strategy

Prospective subjects will be identified in the Epic medical record at CHOP. Patients with at least 2 asthma exacerbations (hospitalizations, ED visits, or outpatient visits where an oral steroid course was given for asthma) in the last year will be recruited from general pediatrics services. Epic alerts and patient lists will assist research staff in identifying eligible patients. Potential participants will be approached in-person by a trained study team member during the course of their hospital stay, at a hospital follow-up appointment, or by telephone. No more than 125 subjects will be enrolled.

### 7.5.2 Study Information Sheet

The study information sheet will be used as a recruitment tool to give participants information about our study. It includes a brief overview of our study and our contact information for potentially interested subjects to contact us.

## 7.6 Informed Consent/Assent and HIPAA Authorization

Subjects will be approached in person while in the hospital, at a hospital follow-up appointment, or by telephone and given information about the study by a trained study team member. Potential participants will not need to decide on participation right away; they may decide whether or not to participate up until the time of discharge from the hospital or end of their follow-up appointment.

Electronic consent via the REDCap platform or written consent on a physical copy of the form will be obtained following agreement to participate in the study.

To reduce low literacy barriers, the study team member will go through the consent form with the family and answer any questions pertaining to the material. Participants will be given 10-15 minutes to review the consent form on their own. This process will be done in a HIPAA compliant manner.

Assent will be obtained for children aged seven or older, as per the CHOP IRB regulations via the REDCap electronic consent platform or on a physical copy of the consent form. The study will be explained in an age-appropriate manner. This process will be done in a HIPAA compliant manner.

### 7.6.1 Partial Waiver/alteration of HIPAA Authorization

We request a partial waiver of HIPAA authorization under 45 CFR 164.512(i.)(2)(ii).

Study staff propose to assess patient eligibility by screening the daily census of patients admitted to a General Pediatrics service at CHOP for patients 5-12 who have an admission diagnosis of asthma and for whom the asthma pathway order is activated using the Epic medical record.

(A) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on the following elements:

1.) Plan to protect the identifiers from improper use and disclosure:

Only authorized study staff will access the Epic medical record for screening purposes. Information from the screening will be stored in a REDCap database only used by study staff.

2.) Plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research:

For those who do not consent to study inclusion, protected health information will be deleted upon the family's decline or if the family is not enrolled in the study for other reasons (unable to approach parent for consent due to lack of parental availability). For those who do consent to be enrolled in the study, HIPAA authorization for the collection of PHI will be obtained at the time of enrollment.

3.) Protected health information will not be reused or disclosed:

Protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted.

(B) The research could not practicably be conducted without a partial waiver of HIPAA authorization.

There are over 2500 admissions for asthma on yearly basis at CHOP with hospital lengths of stay generally less than 24-48 hours, and each of these cases could be potentially eligible for recruitment. Given the limited time each patient is in the hospital and the number of potential patients, it would not be feasible to consent each of these 2500 for screening of their electronic medical records for eligibility.

(C) The research could not practicably be conducted without access to and use of the protected health information.

Access to protected health information is necessary in order to assess eligibility for the study. For example, protected health information would be used to identify current inpatients, screen for eligible ages based on our inclusion criteria, subject's date of admission, primary care doctor, and whether the subject has been prescribed the specific daily controller medications which are compatible with the electronic monitoring devices.

### 7.6.2 Waiver of Consent

We request a Waiver of Consent under 45 CFR 46.116(d).

Study staff propose to assess patient eligibility by screening the daily census of patients admitted to a General Pediatrics service at CHOP for patients 5-12 who have at least 2 admissions for asthma OR 1 admission AND at least 1 ED visit in the last 365 days using the Epic medical record and Epic alerts and patient lists.

The research meets the criteria for a Waiver of Consent based on the following elements:

(A) The research involves no more than minimal risks to the subjects, based on the following 3 elements:

1.) Plan to protect the identifiers from improper use and disclosure:

Only authorized study staff will access the Epic medical record for screening purposes. Information from the screening will be stored in a REDCap database only used by study staff.2.) Plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research:

For those who do not consent to study inclusion, protected health information will be destroyed upon the family's decline or if the family is not enrolled in the study for other reasons (unable to approach parent for consent due to lack of parental availability). For those who do consent to be enrolled in the study, HIPAA authorization for the collection of PHI will be obtained at the time of enrollment via informed consent.

3.) Protected health information will not be reused or disclosed:

Protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted.

(B) The waiver will not adversely affect the rights and welfare of the subjects:

When potential participants are determined to be eligible for enrollment, a study team member will explain the study and ask if they would like to participate. Consent will be obtained in a HIPAA compliant manner, as described in the study procedures (see above Section 9.6). Participants will retain the right to choose whether they want to participate and provide consent. Patients who are deemed ineligible based on screening of the Epic medical record will not be approached for enrollment. The only information that will be retained for those screened ineligible will be the reason why they were deemed ineligible.

(C) The research could not practicably be carried out without the waiver:

There are over 2500 admissions for asthma on yearly basis at CHOP with hospital lengths of stay generally less than 24-48 hours, and each of these cases could be potentially eligible for recruitment. Given the limited time each patient is in the hospital and the number of potential patients, it would not be feasible to consent each of these 2500 for screening of their electronic medical records.

(D) Whenever appropriate, the subjects will be provided with additional pertinent information about participation.

Following screening using the Epic medical record, potentially eligible subjects will have the opportunity to review the study consent form and ask questions of the study team member. The Principal Investigator may also be contacted by phone if more information is needed. The consent form includes contact information, and the participants may request additional information at any time. Patients who are deemed ineligible based on screening of the Epic

medical record will not be approached for enrollment and only the reason for study ineligibility will be retained.

## 7.7 Payment to Subjects/Families

7.7.1 Compensation

Non-responders who do not undergo randomization will receive a $10 disbursement for their participation and not be paid further. At the completion of Visit 1, caregiver study participants will receive an automatic debit card credited with $20. For participants who are enrolled by telephone, they will be mailed their automatic debit card following enrollment. At the end of Study Visits 2, 3, 4, and 5, caregiver participants will be credited $20 for each study visit, for a total of $100. Additionally, children in Arm 1 will receive a performance-based reward payment during each month of the Experiment phase with a maximum value of $30/month. Children randomized to Arms 2 and 3 who have any actuations recorded each month of the Experiment phase will receive a $10 disbursement at the end of each month (for a total of $30) and children in all study arms will receive a $10 disbursement at the end of each month with recorded actuations during the Observation phase (for an additional $30), none of which will be contingent upon ICS adherence.

# 8 PUBLICATION

Data will be analyzed by the investigators, with the help of a study statistician, and submitted for presentation at national meetings and publication in academic journals.

## 9 REFERENCES

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# Appendix 1

**Run-in phase text messages and automated responses:**

**Text 1:** PARTICIPANT_FIRSTNAME, welcome to the run-in period! We will be sending you a few texts over the next 2 weeks. Please respond to these messages if they ask for a response, otherwise you may be removed from the study. Text 1 to confirm you received this text.

Automated response: Great, thank you!

**Text 2:** Are you having problems with the Propeller sensors or app? Text 1 for YES or 2 for NO.

If 1, automated response: Thank you for your response. A study team member will be contacting you shortly.

If 2, automated response: Great, thank you!

**Text 3:** Is the app getting puff information from the sensors? Text 1 for YES or 2 for NO.

If 1, automated response: Thank you for your response. A study team member will be contacting you shortly.

If 2, automated response: Great, thank you!

**Text 4:** Are you receiving our texts? Text 1 for YES. If you haven't responded to any of our messages, you will be removed from the study. And we want you to stay!

If 1, automated response: Great, thank you!

## Experiment phase text message reminders:

1. Hi! This is your friendly daily controller inhaler reminder. Quick fact: children who take controller medication daily have fewer future asthma attacks.

2. Hello! A friendly reminder to make sure your child took their daily controller inhaler. Even for older children, parents are an important part of improving asthma control.

3. Hi! Did your child take their daily controller inhaler today? Quick fact: when taken regularly, daily controllers reduce the number of emergency room visits.

4. Hello there! Has your child taken all of their daily controller puffs today? Remember to always use a spacer with those puffs.

5. Hi! A quick reminder to make sure that your child took their daily asthma inhaler. Quick tip: have your child take their daily controller inhaler with another daily activity (tooth-brushing).

6. Hi! This is a friendly daily controller inhaler reminder for you. When taken regularly, daily inhalers reduce the number of missed school days.

7. Hello! This is your friendly daily controller inhaler reminder. Quick tip: when your child is away from home remember to send medications and a spacer with them.

8. Hi! Remind your child to take their asthma medicine. Each puff you take (as prescribed) gets you closer to your goal!

9. Hi! Did you remind your child to take their controller inhaler today?

10. Hi there! Make sure to remind your child to take their medicine today!

## Appendix 2: Data Safety and Monitoring Plan

### Study Oversight:

This study will utilize an institutionally-appointed Data Safety and Monitoring Board (DSMB), which will hold DSMB yearly meetings via teleconference. The DSMB will be responsible for monitoring any data and/or safety issues and also providing recommendations as needed for the following:

- Participant safety
- Initial approval of the protocol and consent forms and subsequent amendments for human subject safety and research ethics
- Data and statistical analysis plan
- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Notification of and referral for abnormal findings

### Study Monitoring:

The data to be presented to the DSMB for review will be proposed at the first DSMB meeting and then provided in aggregate at subsequent meetings. At a minimum, recruitment and retention data, baseline characteristics, changes to the protocol and consent or planned analysis, and the following outcome data will be included: asthma medication adherence and asthma-related healthcare utilization. In addition, data quality (timeliness and completeness of data collection, resolution of discrepancies), safety data (adverse events (AEs), serious adverse events (SAEs), and unanticipated problems), and study conduct (protocol deviations) will also be included.

Ongoing monitoring of recruitment will be tracked using a master screening log stored on the study's Way to Health database at the University of Pennsylvania. Way to Health is an NIH-sponsored, web-based platform that automates many of the research functions necessary for conducting randomized controlled trials of behavioral incentives.

Monitoring of data collection will be performed by the research project manager and research assistant:

- Monthly review of adherence data from Way to Health
- Monthly review of EHR data on asthma-related ED visits and hospitalizations

Missing data will be managed by running twice monthly data query reports in the Way to Health database. Data discrepancies will be resolved by the study research assistant and other study staff with corrections and/or comments entered into the Way to Health database within one week of receiving data query.

Protocol deviations will be identified by PI and research project manager and reported to the CHOP IRB through the electronic IRB reporting system in accordance with CHOP IRB policy. These events will be presented to the DSMB and reported to the research team at regularly scheduled study meetings.

**Safety Monitoring:**

An adverse event (AE) includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Results in a persistent or significant disability/incapacity
- Results in in-patient hospitalization or prolongation of existing hospitalization
- Results in a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

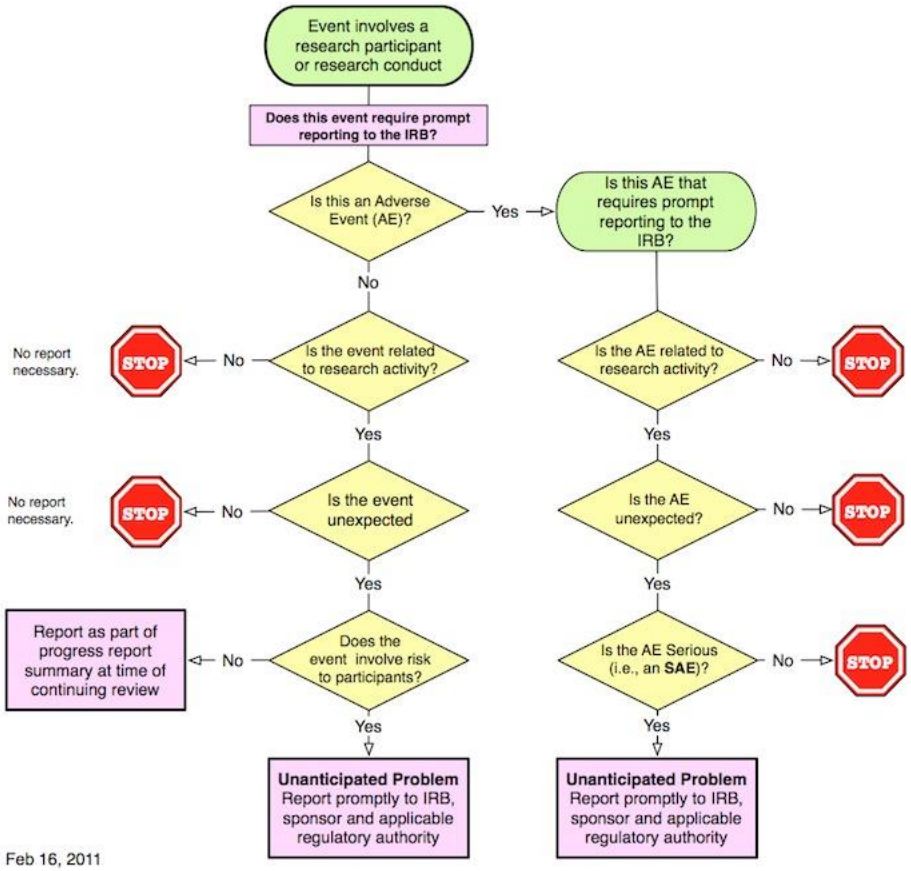
Safety data collection:

Information regarding unanticipated problems and adverse events (AE) and serious adverse events (SAE) will be collected at each study visit through follow-up questionnaires. Once the adverse event has been identified, determined to be unexpected, and at least potentially related to the research study, appropriate CHOP IRB electronic forms will be completed and submitted to the IRB.

Safety data reporting:

Events identified will be recorded and reported to the CHOP IRB. These events will be presented to the DSMB and reported to the research team at regularly scheduled study meetings. Led by the PI, the research team will review each event and make appropriate safety decisions.

SAEs will be communicated by the research personnel immediately to the PI. For SAEs that are determined to be unexpected and at least potentially related to the research study, the study PI will notify the IRB committee assigned to this project at Children's Hospital of Philadelphia, as well as the study DSMB, within 48 hours of first knowledge of the SAE. The IRB and DSMB's assessments of such an event will then be forwarded to the NHLBI within 15 calendar days, as outlined in the "Reportable Events" table below. Because most enrolled patients will have moderate or severe asthma requiring hospitalization in the past, hospitalizations are expected to occur. All AEs (including SAEs) will be followed to their conclusion or stability, with necessary management recorded. Additional details for reporting unanticipated problems, AEs, and SAEs are detailed at the following CHOP Office of Regulatory Affairs website: https://irb.research.chop.edu/reportable-events and in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. The flowchart depicted below will be used to make assessments regarding the way the incident will be characterized for reporting.




AEs and unanticipated problems will be summarized in narrative or other format and submitted to the IRB at the time of continuing review. This information will also be reported to NHLBI during the annual progress report. See below for a table which documents the reportable events and when they will be reported to the CHOP IRB, NHLBI, and by whom.

| Reportable Event | When Reported to CHOP IRB | When Reported to NHLBI | Reported by Whom |
|---|---|---|---|
| IRB suspension or study termination | | 3 calendar days from initial receipt of information | CHOP/PI |
| Study related death or life-threatening event | Within 48 hours of discovery | 7 calendar days from initial receipt of information | PI |
| Unexpected SAE related to study | Within 48 hours of discovery | 15 calendar days from initial receipt of information | PI |
| Unanticipated problems that are not SAEs | 7 calendar days | 15 calendar days from PI becoming aware of the problem | PI |
| Serious or continuing non-compliance | | 10 calendar days | CHOP |
| AE/SAEs determined not to be related to the study | Annual continuing review | Annual progress report | PI |
| Minor Protocol deviations (Determined not to be unanticipated problems) | Annual continuing review | Annual progress report | PI |

Reproduced from https://www.nhlbi.nih.gov/research/funding/human-subjects/adverse-event

Subjects who experience an SAE will be allowed to continue participation in the study. SAE management will be provided by the clinical teams that care for the participants with input from the PI on how medication adherence may have influenced the ED visit or hospitalization.

**Risks and Benefits:**

Potential risks of trial participation: While the child's usual asthma care may not be minimal risk, risks directly related to study intervention are minimal. There is no risk of discomfort due to the study intervention. The study intervention merely adds electronic monitoring, text message notifications, and nominal financial incentives to already prescribed medications. The main risk is breach of confidentiality. Please refer to the section below on data security and participant confidentiality for the strategies in place to avoid this risk. Upon enrollment, the study team will emphasize to study

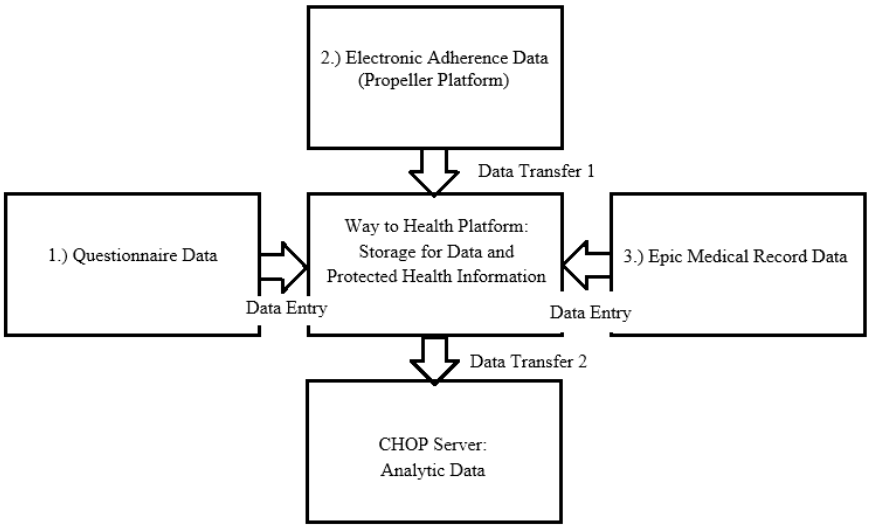
participants that the trial's activities are not clinical care and that study participants should follow the clinical recommendations and care of their clinical providers. This point is included on the study informed consent form and will be emphasized verbally to all study participants.

Potential benefits of trial participation: Participants in this study may experience improvements in their adherence to their daily controller medications. Improved adherence may lead to better control of asthma and therefore decrease school absences, parental work absences, and the number of visits to the ED or admissions to hospitals.

Risk-benefit assessment: The risks of this study are minimal. The main risk of the study is breach of confidentiality. The potential to improve asthma adherence may improve asthma control and decrease ED visits or hospital admissions for asthma. Therefore, potential benefits of study participation outweigh the potential risks.

**Data acquisition, security, and participant confidentiality:**

Data will be obtained from participant surveys, the electronic medical record, and the electronic medication adherence sensors placed on the participants' primary asthma controller and rescue medication. For a summary of data entry and transfer, refer to figure below.




Each study subject will be assigned a study ID at the time of enrollment, which will serve as the means of protecting personal health information during data storage. The master list with study IDs will be kept in a separate CHOP network folder from the datasets and will be eliminated after all publication of findings are completed rendering the datasets deidentified.

Epic medical record and study questionnaire data will be entered directly into the Way to Health platform (in the case of patient identifiable information) or on a paper form during the study visits. Electronic adherence data will be transferred electronically from the respiratory sensor platform to the Way to Health Platform via the respiratory sensor platform API (Application Programming Interface). An additional data transfer will be used to extract the analytic data set to the secure CHOP research server for analysis. All databases created will be password-protected and only study team members will have access. All data sets downloaded through the respiratory sensor or Way to Health platforms will be password-protected and stored on the CHOP secured network drive, only accessible to study team members. Please see study protocol section 7.2 for a full description of data security and patient confidentiality measures in place to protect data transfers and storage on the respiratory sensor and Way to Health platforms, CHOP secured network drives, and the transfers between the platforms and drives.

**Interim analyses and stopping rules:**

Given the minimal risk nature of this study, there are no planned interim analyses or criteria for prematurely stopping the study.

**Reporting:**

Any change to protocol or amendment to protocol will be approved by CHOP IRB prior to putting in place.

Reports, every year, regarding participant accrual, study progress, AEs and SAEs, and data quality will be developed by the research team. Report by unidentified arms will be made available to the study statistician and the DSMB as specified by the trial protocol, Good Clinical Practices, and applicable regulations. Copies of these reports will be made available to the DSMB and NHLBI by the project biostatistician. Reports to the DSMB and the NHLBI will also include any protocol changes or study conduct issues including protocol deviations.

**Conflicts of interest:**

The Principal Investigator and co-Investigators have no conflicts of interest. Each year, research team members will be asked to state whether they have developed any new conflicts of interest since the last formal annual report. The research team will report to the DSMB any new potential conflicts of interest prior to each scheduled meeting.