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Medication Adherence in Pediatric Asthma: A Preliminary Analysis of a Randomized Control Trial using Electronic Monitoring Devices

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Medication Adherence in Pediatric Asthma: A Preliminary Analysis of a Randomized Control Trial using Electronic Monitoring Devices

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Medication Adherence in Pediatric Asthma: A Preliminary Analysis of a Randomized Control Trial using Electronic Monitoring Devices

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INTRODUCTION:

Asthma is the most common chronic disease in children, affecting more than 6.1 million children under the age of 18 in the US (Center for Disease Control, 2015). Asthma is characterized by persistent airway inflammation, hyper-responsiveness to bronchodilators, reversible and variable airflow obstruction which leads to respiratory symptoms that vary in terms of frequency and severity over time (Bonini and Usmani, 2018). Asthma is a significant burden to the healthcare industry, resulting in 439,000 hospitalizations and 1.8 million emergency department (ED) visits, contributing to 3,518 deaths in 2016, 209 of whom where children (CDC, 2016). None-adherence to asthma medication is a common problem in patients with asthma, especially in children, leading to more frequent asthma exacerbations, ED visits and hospital admissions (McGrady and Hommel, 2013). Current methods of assessing for adherence, including self-report and pharmacy record, often overestimate actual adherence, making them unreliable means of supporting clinical decision making (Desai and Oppenheimer, 2011). Electronic monitoring devices (EMDs) are more accurate means of assessing for adherence but are not currently used in practice. The objective of this study was to determine whether a mobile-based reminder system paired with EMDs could improve pediatric asthma medication adherence.

SPECIFIC AIMS:

Pediatric with physician-diagnosed persistent asthma in the Hartford community were recruited into this study to assess the feasibility and utility of EMD technology in this at-risk population. It was hypothesized that by combining a mobile-based reminder system paired with EMDs and patient education through adherence feedback, there would be an increase in adherence to asthma medications in children with persistent asthma.

BACKGROUND -

Optimal asthma management is dependent on adequate control of asthma symptoms, and prevention of exacerbations. Exacerbations require bronchodilator usage and severe exacerbations results in treatment with systemic corticosteroids and may require hospitalization or stays in the intensive care unit (Lasmar et al, 2009). For patients with persistent disease, where symptoms are not relieved with inhaled beta-2 agonists ("reliever" medication) alone, the mainstay of therapy relies on inhaled corticosteroids (ICS), also known as "preventer" or "controller medication". ICSs typically require daily administration to achieve adequate efficacy, along with proper technique and regular dosage timing (Gillette et al, 2016). Adequate adherence to ICSs has been shown to be integral in controlling asthma symptoms as well as in preventing ED visits and hospitalizations (Barnes et al, 2015). Studies have shown that adherence rates of at least 75% - 80% are required for adequate asthma control (Lasmar et al, 2009; Williams et al, 2011). Yet, extensive studies report suboptimal adherence rates, especially in children, where reported rates of adherence are typically <50% (Engelkes et al, 2015; Morton et al, 2014). Several factors have been shown to contribute to medication non-adherence, including low socioeconomic status, low literacy, medication cost, access to care, language barriers, as well as parent-child relationships (Bidwal et al, 2016; Burgess et al, 2011).

Poor adherence to anti-inflammatory therapy in the form of ICS is associated with significant asthma morbidity and mortality (Milgrom et al, 2002; Milgrom et al, 1996; Cote et al, 2003). Non-adherence to asthma medication leads to overuse of reliever medication and more frequent severe asthma exacerbations, leading to more frequent ED visits and hospital admissions, resulting in increased healthcare utilization and cost (Puranik et al, 2016, McGrady and Hommel, 2013). Additionally, children with poor adherence are more likely to have

worsened lung function (Morton et al, 2014). A recent report from the United Kingdom demonstrated that 34% of deaths due to asthma are associated with poor adherence, further emphasizing the significance of this problem (Royal College of Physicians, 2014). While various interventional studies have been conducted on asthma medication adherence in children, many studies are limited by the subjective nature of measurements for adherence (Desai and Oppenheimer, 2011). A recent review found that a major limiting factor to clinical trials on severe asthma is an inadequate assessment of adherence to maintenance therapy, resulting in increased costs of trials as well as loss of statistical power (Mokoka et al, 2019). Self-reported adherence to asthma medication, which is the most common way to assess adherence in research studies, often overestimates medication adherence, making accurate assessment and intervention difficult for clinicians (Bender et al, 2004, Burgess et al, 2008). In one study on inner-city children, parents' report on their child's adherence to asthma medications was 85%, compared with <25% when measured using pharmacy refill records (Otsuki et al, 2009). Outside of verbal reports of adherence, questionnaires and diaries have also been employed to quantify and potentially standardize adherence rates. However, these methods have also been shown to overestimate actual adherence (Lam and Fresco, 2015). Other, more quantitative methods, such as weighing canisters, dose counters on inhalers, and calculating medication possession ratio using prescription refill data have all been studied as more objective ways of monitoring adherence. However, the reported adherence from each method varies greatly, and none can accurately measure true consumption of medications (Bender et al, 2000, Krishnan et al, 2012, Sumino et al, 2013, Chung et al, 2000). Furthermore, physician judgment of patient adherence, a key component to understanding disease management and optimizing treatment planning, is also inaccurate (Pearce and Fleming, 2018).

The usage of electronic monitoring devices (EMDs) offers a much more accurate and objective view of adherence and has since been proposed as the possible "gold standard" for measuring adherence due to its ability to offer time-sensitive information (Riekert and Rand, 2002). Studies that compare usage of EMDs against other forms of adherence measurements consistently find that EMDs are more accurate and provide adherence rates that are much lower than traditional means of measuring adherence (Bender et al, 2000; Riekert and Rand, 2002; Pilcher et al, 2015). Though there is variability in the design and implementation of these EMDs, most share common features, including a sensor to track actuations of inhalers, ability to track doses using some form of sync function, and the ability to access adherence data for patients and/or clinicians (Chan et al, 2015). One of the earliest EMDs introduced in clinical trial was Doser, which was made commercially available in 1997. Despite clinical trials validating the accuracy of this technology against other means such as canister weighing, as well as relative low cost, the Doser is not commonly used in clinical practice today (Simmons et al, 1998; O'Connor et al, 2004). Thus, despite clear advantages in measuring adherence rates, these devices are not routinely used as part of interventions geared to improve medication adherence, likely due to the cost associated with implementing such technology in the general public. Additionally, lack of consistent research showing improved health outcomes have limited uptake of insurance coverage for EMDs.

Recently, a growing body of literature on mobile technologies and remote patient monitoring have been proposed as cost-effective ways of improving medication adherence in chronic diseases, especially in children and adolescents (Van Gaalen et al, 2012; Mulvaney et al, 2013; Fedele et al, 2017). In this age group, self-management of asthma, which includes not only adherence to medications, but also behaviors to monitor and prevent symptoms such as avoiding

asthma triggers, are often limited in scope (Bruzzese et al, 2012). Thus, technologic interventions offer a potentially viable modality of behavioral change, especially in the management of asthma. A number of studies have shown improvements in medication adherence through incorporation of electronic reminders using text message reminders (Petrie et al, 2012; Britto et al, 2017; Vasbinder et al, 2016). A pilot study done at the University of Cincinnati (n = 62) looked at the effects of text message reminders over 3 months and found that there was an initial 2.75% increase in adherence compared to baseline as measured by EMDs. However, such a difference was not sustainable by the end of the study (Britto et al, 2017). In a multicenter RCT, another study looked at the utilization of short text message reminders on adherence to ICS in children ages 4 - 11 over a span of 12 months. Text message reminders were sent to parents and children, if they possessed a mobile phone, when missed doses were recorded using EMDs. The study found that mean adherence over the total period of the study was higher in the intervention vs control (69.3% vs 57.3%) as measured by EMDs. While there was a significantly higher rate of adherence within the first six months, such high rates did not persist during the remainder of the study period. Additionally, it found no differences in asthma control, quality of life, or asthma exacerbations (Vasbinder et al, 2016). Another study conducted in New Zealand (n = 216) also looked at the effects of a text message reminder system on adherence to asthma medications in adults aged 16 – 45. The study found that the intervention group had a higher average rate of self-reported adherence when compared to control (57.8% vs 43.2%). A key limiting factor to this study was the reliance on self-reported adherence. While these studies show some promise in increasing adherence rates immediately after initiation of the intervention, they demonstrated that simple reminder systems may be inadequate in addressing long-term behavioral changes (Apter et al, 2012).

While the concept of utilizing EMDs in management of asthma is not a new concept, the integration of this technology into clinical practice has not been extensively studied. In studies looking at the accuracy of utilizing inhaler trackers, they have shown consistently high accuracy and reliability (Bonini and Usmani, 2018). In the pediatric population, studies have assessed changes in asthma adherence after utilization of EMDs, often in concert with electronic reminders and/or clinician feedback. However, most studies are small in study size and short in clinical follow up. One study (total n = 26) assessed the usage if an EMD along with adherence feedback and found that adherence was significantly higher in the intervention group (79% vs 58%) after four months. A study with a larger study size (n = 90) assessed the role of EMDs, daily reminder alarms along with adherence feedback found significantly improved adherence in the intervention group compared to the control (70% vs 49%) but did not find significant differences in asthma control or lung function. Additionally, the EMD utilized was not able to relay real-time adherence information for the participant or the participants' parents until follow-up visits, when adherence information was reviewed for feedback with the clinician (Morton et al, 2016). These studies show that while EMDs may increase adherence, more research is needed to elucidate how EMDs can best be implemented in the clinical setting .

Inherently, the nature of adherence is multifaceted and effective treatment cannot merely rely on reminder systems. Barriers to adherence may be "intentional", such as having doubts or concerns about treatment effectiveness or side effects, or "unintentional", such as forgetfulness and lifestyle barriers (ref). Reminder systems target the unintentional barriers to adherence, but lack the educational intervention needed to target intentional barriers (Foster et al, 2014). While mobile technology offers a unique way to address adherence in real-time, few studies have looked at the effects of a combination of audiovisual reminders and feedback from medical

providers on patient adherence in order to address intentional barriers to adherence. Feedback alone has been shown to increase adherence, but such studies are limited by the size of study sample (Onyirimba et al, 2003; Spaulding et al, 2012). In a systematic review of interventions intended to improve adherence to inhaler medications in chronic lung disease, results indicate that the combination of electronic monitoring with feedback was associated with significant improvement in adherence (Pritchard and Nicholls, 2013). By combining mobile-based reminder alarms with clinician feedback using real-time adherence from EMDs, both unintentional and intentional barriers to adherence can be addressed. Real-time monitoring of adherence provides greater insight regarding medication behaviors for physicians to better understand their patients, creating both the educational opportunity to address both types of barriers to adherence through clinical feedback. Additionally, this creates an opportunity to better direct care coordination efforts in order to address socioeconomic barriers to adherence as well.

Non-adherence to asthma therapy is greatly influenced by socioeconomic factors (Mazumdar et al, 2015). This is especially true in Connecticut, where childhood asthma prevalence is consistently higher than that of the national average (11.3% compared to the national average of 8.2% ref). In Connecticut, the highest prevalence of asthma is in the Hartford community, consistent with national data that shows asthma prevalence is disproportionally high among children from low-income and minority families as well as children that reside in inner-city neighborhoods (Collaborative for Asthma Equity in Children, 2016; Nepaul et al, 2012; Scope et al, 2016). Healthcare utilization due to asthma in children is also significant in this population, resulting in 241.7 ED visits and 41.5 hospitalizations per 10,000 people, which is significantly higher than the national average of 51.7 ED visits and 18.3 hospitalizations per 10,000 people (Collaborative for Asthma Equity in Children, 2016; CDC, 2015). In children with

severe, poorly controlled asthma, poor adherence to ICSs is viewed as an important contributor to poor asthma control resulting in further exacerbations requiring ED visits and hospitalizations. Studies consistently show that lower socioeconomic status is associated with poorer asthma control in children with asthma, with non-adherence adversely affecting those with low income and education levels (Gong et al, 2014; Scope et al, 2016). Adolescents are particularly at risk for non-adherence as asthma mortality in this group is approximately twice that of younger children (Akinbami and Schoendorf, 2002). Self-management of asthma in adolescents is limited, and barriers to achieving adequate control are multifaceted, with contributing factors including lack of patient knowledge of disease, poor understanding of the benefits of medication, forgetfulness, and negative attitude towards asthma (Holley et al, 2017). Currently, most interventions designed to improve adherence in this age group are geared towards educational and behavior modification interventions, including educational materials, individual and group sessions, and follow-up phone calls (Bender et al, 2003). With the advent of EMDs, increasing efforts are geared towards empowering adolescents to gain greater independence through improved self-management of chronic diseases by implementing such technologies.

METHODS:

Study Design -

This study was a prospective, randomized, controlled trial of children with persistent asthma who are managed on daily ICSs. The goal of the study was to enroll 75 children, randomized 2:1 into the intervention arm and the control arm, respectively. Such a sample size was chosen due to the supply of EMDs (50) we had available to use for the study. The study population consisted of children ages 8-17 years old with physician-diagnosed persistent asthma. Participants needed to have been prescribed an ICS for at least one month using a pressurized metered dose inhaler (pMDI) or dry powder inhaler that is compatible with the HeroTracker EMD (Table 1; Figure 2A). The child or the parent/guardian, whoever was the main person who administered the child's medications, must have had a compatible smartphone with Bluetooth capabilities. Patients had to be English or Spanish speaking. Patients with other co-morbidities (including other types of chronic lung disease, chronic medical conditions such as congenital heart disease) were excluded from the study. Patients who were or planned on becoming pregnant were also excluded from the study.

Participants were recruited from the Connecticut Children's Medical Center's (CCMC) Pulmonary clinic in Hartford, Connecticut. Participants were approached to participate during regular visits to the pulmonary clinic. After verification of study eligibility based on inclusion and exclusion criteria, the details of the study were discussed in detail with the child and parent present at the visit. If the parent agrees for the child to participate, written consent from the parent as well as assent from the participant were obtained by study personnel. Participants were then stratified by age at the time of enrollment (8-13 years, 14-17 years), and randomly assigned into the intervention or control group using computer-generated block randomization with block

sizes of three, six, or nine. Due to the nature of the study, the participants, research personnel and the clinicians were not blinded.

After enrollment, each participant was followed at 3 months (+/- 20 days) and at 6 months (+/- 20 days) (Figure 1). The follow up appointments were meant to correlate with regularly scheduled follow up appointments for participants.

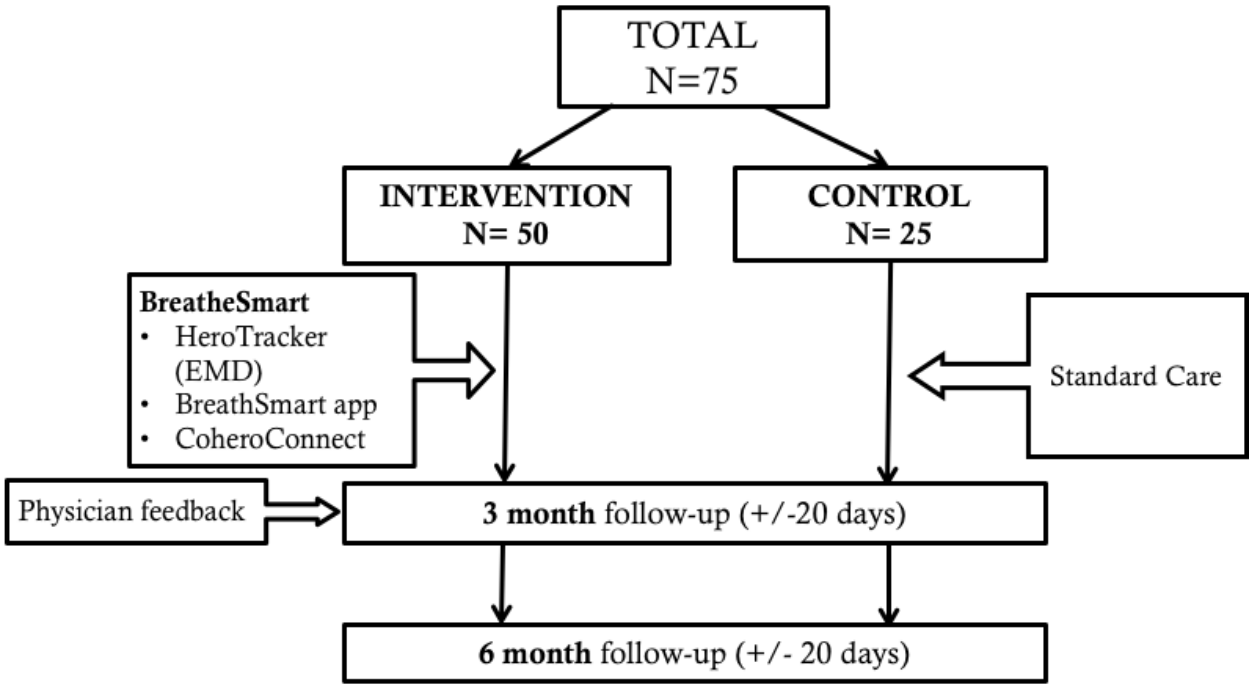

Figure 1. Study Design.

Daily Control	
Advair Diskus (100/50 mg), (250/50 mcg), (500/50 mcg)	Dulera 100/5 mcg and 200/5 mcg
Advair HFA (45/21 mcg), (115/21 mcg), (230/21 mcg)	Duolin HFA 20 mcg
AeroSpan 80 mcg (60 count) and (120 count)	Flovent 44 mcg, 110 mcg and 220 mcg
Alvesco 80 mcg and 160 mcg	Flovent Diskus 50 mcg, 100 mcg and 250 mcg
Asmanex HFA	Foratec HFA 12 mcg
Asthavent 100 mcg	Foster 100/6 mcg
Atimos 12 mcg (50 count), (100 count) and (120 count)	Ipvent HFA 40 mcg
Beclate HFA 50 mcg, 100 mcg, 200 mcg	QVAR 40 mcg, 80 mcg
Budeflam 100 mcg	Serevent Diskus
Ciclovent 160 mcg	Seroflo 50 mcg,125 mcg, 250 mcg
Clenil 50 mcg, 100 mcg, 200 mcg, 250 mcg	Symbicort 80/4.5 mcg, 160/4.5 mcg, 400/12 mcg
Rescue	
Atrovent HFA	
ProAir HFA	
Proventil HFA	
Ventolin HFA 60 count, 200 count	
Xopenex HFA 80 count, 200 count	

Table 1. Pressurized metered dose inhalers (pMDI) compatible with the HeroTracker EMD.

Intervention Group:

The intervention arm consisted of a mobile-based platform produced by Cohero Health® that consists of: 1) BreatheSmart mobile application, which tracks medication usage and sends real time reminders based on individual treatment plans, 2) HeroTracker sensor, which is an EMD that counts actuation of the inhaler it is attached to, and is synced to the BreatheSmart app via Bluetooth technology, and 3) CoheroConnect, a HIPPA-compliant, web-based portal that allows researchers and clinicians, to monitor adherence in real-time (Figure 2). Using these three products, participants received alerts through their BreatheSmart app to take their daily preventive ICSs, which were typically given once daily or twice daily. Participants were given two HeroTracker sensors, one for the controller (ICS) and another for the rescue (albuterol) MDIs, allowing the app to track actuation for both types of inhalers. Study personnel along with clinicians were trained on how to monitor adherence using CoheroConnect. If randomized into the intervention arm of the study, the participant and/or the parent (whomever was the main person managing the participant's daily ICS) were provided with training on how to utilize the BreatheSmart app at the initial intake visit. Participants were told to download the app while in the office and were instructed on how to sync their HeroTrackers to their phones. If participants were unable to do this in the office, study personnel contacted the participants after the visit to ensure participants did not have any issues with the installation process.

At the 3-month follow up visit, physicians are asked to review adherence data since the participant's previous visit via CoheroConnect and provided adherence feedback to the participant. Each feedback discussion by the physician was personalized to the participant and the participant's level of adherence.

A)

B)

Figure 2. Components of BreatheSmart Intervention. A) HeroTrackers – wireless Blue-tooth enabled inhaled sensors that are attachable to pMDI (left) and diskus (right) inhalers. B) CoheroConnect– a web-based platform for clinicians to monitor participants' adherences.

Control Group:

Control participants were provided standard care as they would be given at a specialized clinic. They were not provided access to the BreatheSmart app, CoheroConnect, or an EMD. Participants were seen at their standard asthma clinic for regular follow up care.

Assessments:

At each visit (initial enrollment, 3-month follow up, and 6-month follow up), the following assessments will be performed:

- **Intake assessment:**
    - Demographics:
        - Age of the participant
        - Ethnicity as defined by the participant and/or parent, characterized into "African American", "White", "Hispanic, non-Puerto Rican", "Puerto Rican" or "Other". During analysis, this was recoded into "African American", "Non-Hispanic White", with "Hispanic, non-Puerto Rican" and "Puerto Rican" recoded as "Hispanic".
        - Gender as defined by the participant, measured dichotomously as "Female" or "Male"
        - Self-reported family income, characterized as "<$15,000", "$15,000-$29,999", "$30,000 – $49,999", and ">$50,000". During analysis, this was recoded into "<$30,000" or ">$30,000"
        - Type of insurance, confirmed using electronic medical records
    - Medication list, and other potential comorbidities
    - Asthma therapy – ICS prescribed, dosage, and frequency of dosage
    - Asthma severity (physician confirmed)

- Asthma Control Test (ACT) score - The Asthma Control Test (ACT) is used to assess asthma control within the past four weeks – a score <= 19 indicates poorly controlled disease (Liu et al, 2006)
- Three methods of assessing for adherence:
    - Test of the Adherence to Inhalers (TAI) – a validated questionnaire to assess for adherence (Plaza et al, 2016)
    - Self-reported adherence, which was reported by the participant and/or parent as the "number of doses missed per week"
    - Pharmacy refill history over the past 6 months prior to enrollment
- Any ED visits in the past year, measured dichotomously as "Yes" or "No"
- Any hospitalizations in the past year, measured dichotomously as "Yes" or "No"
- Any oral steroid use in the past year, measured dichotomously as "Yes" or "No"
- Pulmonary Function Test (PFTs), including Forced Expiratory Volume (FEV1) and Fractional exhaled Nitric Oxide (FeNO), which were confirmed using electronic medical records.
    - FEV1% <= 80% indicates "Not well controlled" asthma based on National Heart, Lung, and Blood Institute (NHLBI) guidelines (National Asthma Education and Prevention Program, 2007)
    - FeNO is a measure of responsiveness to anti-inflammatory therapy, but is not clinically indicated for every patient. FeNO > 50 ppb (>35 ppb in children < 12 years of age) indicates low-adherence or inadequate response to ICS based on American Thoracic Society (ATS) guidelines (Dweik et al, 2011)

- **Follow-up assessment:**
    - ACT score
    - TAI
    - Self-reported medication adherence
    - Pharmacy refill history since last visit
    - Number of ED visits since last visit
    - Number of hospitalizations since last visit
    - Number of oral steroid uses since last visit
    - PFTs, including FEV1 and FeNO
    - For intervention group –
        - Any technical issues related to the BreatheSmart platform
        - For those who completed six months in the study, participants were asked to answer a 5-item questionnaire which was scored on a 5-point semantic differential scale (1 = strongly disagree, 5 = strongly agree) which asked about topics such as acceptability of use, perceived effects on asthma control, and usefulness of physician feedback:
            - "I would be happy to continue using my BreatheSmart app and HeroTracker"
            - "I feel more control of my asthma now"
            - "Knowing when to take my asthma medication is easy"
            - "I would recommend using this to other people I know with asthma"
            - "Going over how often I take my asthma medication with my doctor was helpful"

Study Outcomes

The primary outcome for this study was medication adherence as measured by pharmacy refill. This was used because this is the most reliable means of measuring adherence between the control and intervention groups. Medication adherence as measured by pharmacy refills was calculated using Proportion of Days Covered (PDC), a commonly used method of calculating adherence that is defined as a ratio of sum of unique days supplied based on refills over the total number of days in the period that is assessed (Choudhry et al, 2010). PDC has been shown to be more accurate at assessing adherence when compared to other methods (Martin et al, 2009). For the baseline adherence measurement, the PDC was assessed over a 6-month period prior to the enrollment date. The 6-month PDC was calculated over the 6-month period from the date of enrollment. Change in PDC was calculated as the difference between the 6-month PDC and baseline PDC.

A secondary outcome for this study was adherence as measure by EMD. Average adherence based on EMD is calculated using the average of daily adherence rates as recorded by the EMDs. Another secondary outcome is the Asthma Medication Ratio (AMR), which is a National Committee for Quality Assurance measurement for patients with persistent asthma. Using pharmacy refill data, AMR is calculated as the ratio of controller refills over the sum of controller refills and short-acting beta-agonist refills. Studies have shown AMR < 0.5 is associated with increased ED visits and hospitalizations as well as poorer quality of life (Beck et al, 2015; Andrews et al, 2013). Other secondary outcomes, such as ACT score, PFTs, TAI, as well as number of ED visits, hospitalizations, oral steroid uses, were evaluated but not presented in this analysis due to low number of responses.

Study Timeline:

The original study protocol was submitted for full board review through the Institutional Review Board (IRB) at Connecticut Children's Medical Center on April 10, 2017. The protocol was approved by the IRB board on July 13, 2017. Recruitment started in January, 2018. Recruitment took place at the Connecticut Children's Medical Center pulmonary clinic in Hartford, Connecticut.

Data and Analysis:

Because this is an ongoing study, we included in the analysis all participants who had been enrolled for six months as of February 1, 2019.

Data analysis was based on an intention to treat model. Medication adherence based on pharmacy refill was calculated using PDC, for which the calculation has been defined elsewhere in literature (Choudhry et al, 2010). Medication adherence rates based on EMD was calculated over the span of the 6-month period, subdivided into morning and night doses, and recorded as a percentage. This was calculated as the ratio of doses actuated as recorded by the EMD over the number of doses prescribed x 100. The daily adherence was capped at 100%, to avoid falsely increased values due to dose dumping. The overall six monthly figure was a mean of each daily %. For example, if a child was prescribed two puffs twice a day, and only took two puffs on the first day, six puffs on the second day, four puffs on the third day, and two puffs on the fourth day, the daily adherence would be 50%, 100%, 100%, 50%, respectively. The average adherence for this time period would be 75%.

Between-group comparisons of adherence rates based on PDC at baseline and at six months were conducted using two-sample independent t-tests. To account for differences in

baseline adherence, changes in adherence from baseline to six months were compared between groups using a two-sample independent t-test. Average EMD adherence rates for the first 30 days, 90 days, and 180 days of the study period were calculated for the intervention group. Additionally, AM and PM EMD adherence rates were calculated and compared using a paired t-test. Changes in AMR (<0.5 or ≥ 0.5) from baseline to 6-months within groups were tested by McNemar test. Chi-square tests were applied to compare AMR between groups at baseline and at six months. All the statistical analyses were performed in SPSS. A *p*-value smaller than 0.5 was considered statistically significant.

RESULTS:

From January 2018 through February 2019, 116 individuals were approached and screened for eligibility to participate. Forty-three (37%) did not meet inclusion criteria and 19 (16%) were not interested. A total of 53 participants (36 intervention, 16 control) were enrolled between January 2018 and February 2019. A total of 41 participants (29 intervention, 12 control) who had been enrolled for six months were included for this analysis. Within the control group, only four participants (33%) completed a 3-month follow up, and only five participants (42%) completed a 6–month follow up visit. Within the intervention group, only 13 participants (45%) completed a 3-month follow-up, and only 16 participants (55%) completed a 6-month follow-up, (Figure 2). This occurred due to either participants not attending or cancelling scheduled appointments. For those without a 3-month follow-up in the intervention group, no physician feedback was provided.

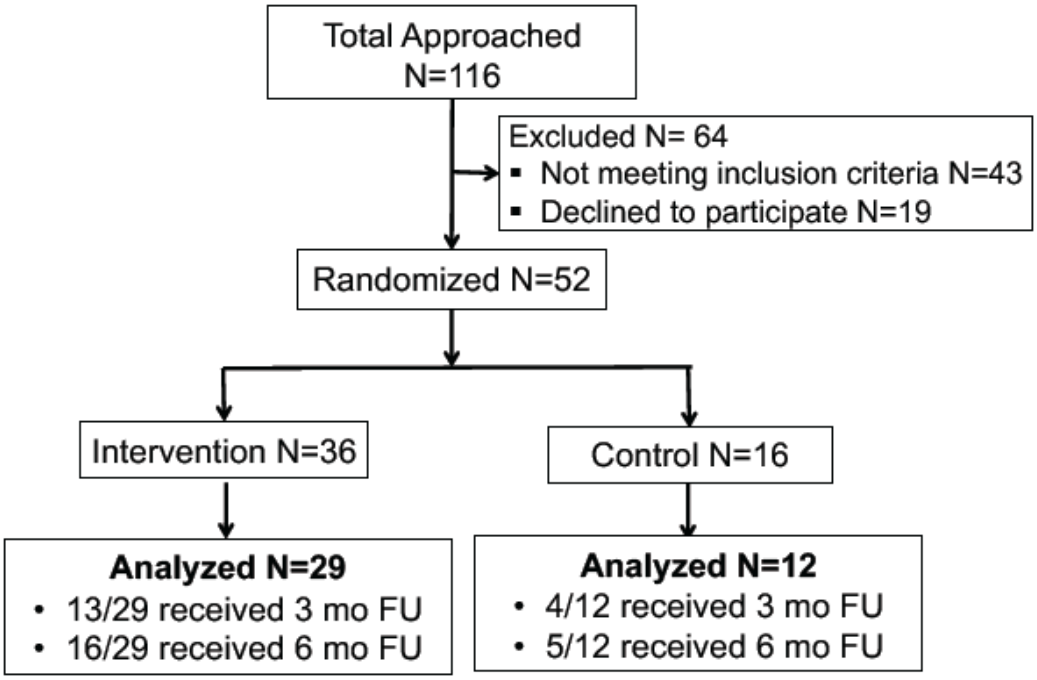

Figure 2. CONSORT diagram (updated on 2/1/2019). Participants who were enrolled in the study for 6 months at the time of analysis are included for this analysis.

Demographics:

Demographic characteristics of participants analyzed are shown in Table 2. Participants were on average 12.7 (SD = 3) years old, 49% were Latino, 29% were Non-Hispanic White, and 22% were African America. The majority of participants (78%) utilized public insurance and slightly more than half reported a family income of less than $30,000. The majority of participants had moderate or severe persistent asthma (44% and 51%, respectively).

	Total (n=41)	**Control (n=12)**	**Intervention (n=29)**	***P* value**
Age (years)	12.7 (3)	12.5 (2.9)	12.7 (3.1)	0.83
Sex (Female)	23 (55%)	6 (50%)	17 (59%)	0.43
Race/Ethnicity				
African American	9 (22%)	4 (33%)	5 (17%)	0.53
Latino	20 (49%)	5 (42%)	15 (52%)	
Non-Hispanic White	12 (29%)	3 (25%)	9 (31%)	
Public Insurance	32 (78%)	11 (92%)	21 (72%)	0.18
Reported Family Income				
<$30,000/year	22 (54%)	8 (67%)	14 (48%)	0.28
>=$30,000/year	19 (46%)	4 (33%)	15 (52%)	
Asthma Severity				
Mild persistent	2 (5%)	1 (8%)	1 (3%)	0.80
Moderate Persistent	18 (44%)	5 (42%)	13 (45%)	
Severe Persistent	21 (51%)	6 (50%)	13 (52%)	

Table 2. Demographics of study participants. Data presented as mean (SD) or N (%).

At baseline, participants had a high disease burden of asthma, as indicated by high rates of ED visits (56%), hospitalizations (34%), and oral steroid usage (80%) in the last year (Table 3). Twenty-two (51%) of the participants had ACT scores <= 19, indicating poor control. Average FEV1% was 90.9%, with 31% of total participants having "Not well controlled" asthma based on NHLBI guidelines. For the participants with FeNO (n= 13), average FeNO level was 51.4 ppb, with 50% of participants showing high levels of FeNO as defined by ATS guidelines (Dweik et al, 2011). At baseline, 66% of patients scored in the "poor" adherence category based on TAI. When asked specifically asked the question "number of missed doses per week", adherence per patient report was 85.8%.

	Total (N=41)	Control (N = 12)	Intervention (N=29)	*P* value
Any ED visits in the last year (N (%))	23 (56%)	7 (58%)	16 (55%)	0.57
Any hospitalizations in the last year (N (%))	14 (34%)	3 (25%)	11 (38%)	0.34
Any oral steroid use in the last year (N (%))	32 (80%)	8 (73%)	24 (83%)	0.38
Baseline ACT score ≤19 (N (%))	22 (51%)	9 (75%)	13 (45%)	0.08
Lung function				
FEV1 <= 80% (N (%))	12 (31%)	1 (10%) (n = 10)	11 (38%) (n = 29)	0.13
High FeNO (N (%))	6 (50%)	2 (50%) (n=4)	4 (50%) (n=8)	0.73
Self-reported adherence (mean (SD))	85.8% (16)	90% (12)	84% (18)	0.65*
Baseline TAI (N (%))				
Good	6 (15%)	2 (17%)	4 (14%)	0.94
Intermediate	8 (20%)	2 (17%)	6 (22%)	
Poor	27 (66%)	8 (66%)	19 (66%)	

Table 3. Baseline characteristics of participants. ACT = Asthma control test (≤19 indicates uncontrolled asthma). FEV1% = Forced expiratory volume in 1 second, % of predicted. FEF 25-75% = Forced expiratory flow at 25-75%, % of predicted. FeNo = Fractional exhaled nitric oxide. TAI = Test of the Adherence to Inhalers. *Due to negative skewness of results, non-parametric Mann-Whitney U test was used to test for null-hypothesis.

Primary Outcome

Adherence rates at six months based on PDC did not differ significantly between the control and intervention groups (Figure 3, $p = 0.21$). The average adherence in both intervention and control groups decreased from baseline to six months. At baseline, the mean adherence based on pharmacy refill for the control group and intervention group was 42% and 50%, respectively ($p = 0.37$). At six months after enrollment, the mean adherence for the control group and intervention group was 31% and 41%, respectively ($p = 0.21$). The adherence for the control group dropped on average by 11%, which was not significantly different from 9% for the intervention group ($p = 0.83$) (Table 4).

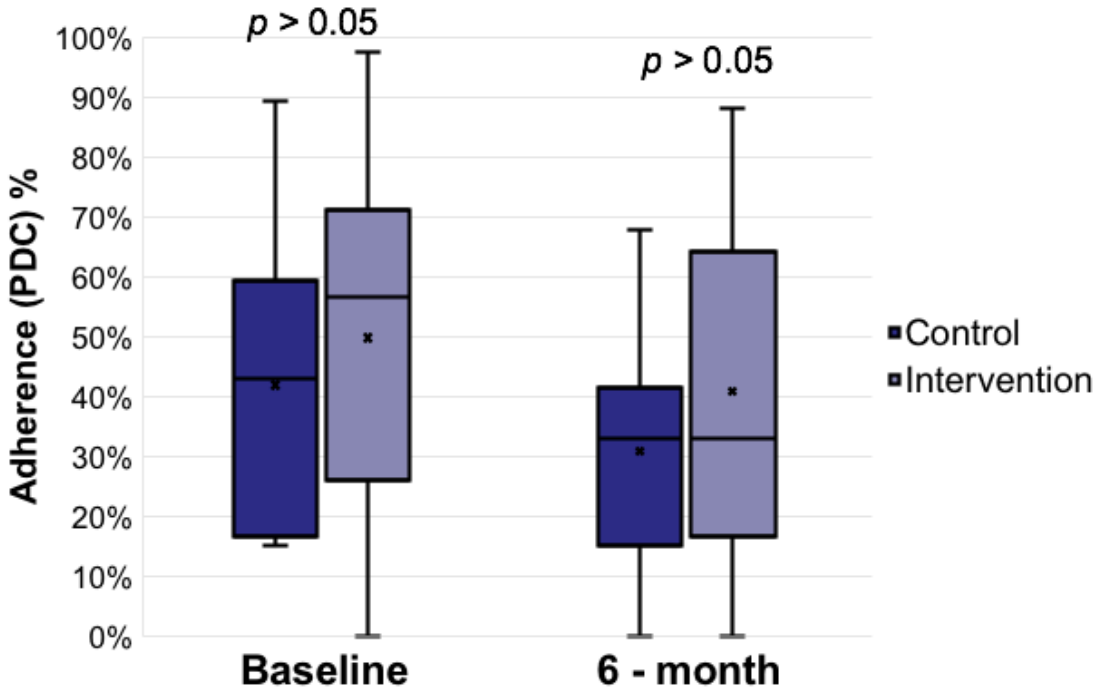

Figure 3. Adherence based on pharmacy refill.

	Control (n=12)	Intervention (n=29)	*P* value
PDC (mean (SD))			
Baseline	42% (24)	50% (27)	0.37
6 months	31% (20)	41% (27)	0.21
Change in PDC (mean (SD))	- 11% (22)	- 9% (32)	0.83

Figure 4. Mean adherence rates based on pharmacy refill.

Secondary outcomes:

Average adherence over the six months for the intervention group was 27.4% based on EMD. Higher average adherence was obtained in the initial 30 days after enrollment (56.1%), but this declined over time during the 6 month study period (Table 5). Of note, out of the 29 patients in the intervention group, only 26 participants were assessed as three participants never used the EMD. Interestingly, when average daily adherence was plotted over time, there was an initial high rate of adherence of > 70% in the first week of the study, but this number dropped drastically after the first week (Figure 4). When comparing average adherence in the first month vs the overall adherence over the six months of the study, there was a statistically significant drop in adherence from 56.1% to 27.4% ($p = 0.00$). When daily adherence was further subdivided into AM and PM doses, there was no difference in adherence to the AM or PM doses (Table 5, $p = 0.22$ for the 180-day adherence).

AMR did not differ significantly between intervention and control groups at baseline or at six months (Table 6, $p = 0.73$ and $p = 1.00$, respectively). McNemar Test also did not show any statistically significant changes in AMR from baseline to six months within the intervention group or the control group ($p = 0.78$ and $p = 0.69$, respectively).

	Average Daily Adherence	Average AM Adherence	Average PM Adherence	*P*-value*
30 Day Adherence (mean, ±SD)	56.1% (35.1)	55.6% (34.7)	54.2% (36.6)	0.64
90 Day Adherence (mean, ±SD)	41.2% (32.5)	39.2% (31.8)	42.4% (35.6)	0.40
180 Day Adherence (mean, ±SD)	27.4% (27.4)	31.8 (33%)	26.2% (27.1)	0.22
**p*-value is calculated as difference between AM and PM adherence rates				

Table 5. Average, AM, and PM adherence rates based on EMDs.

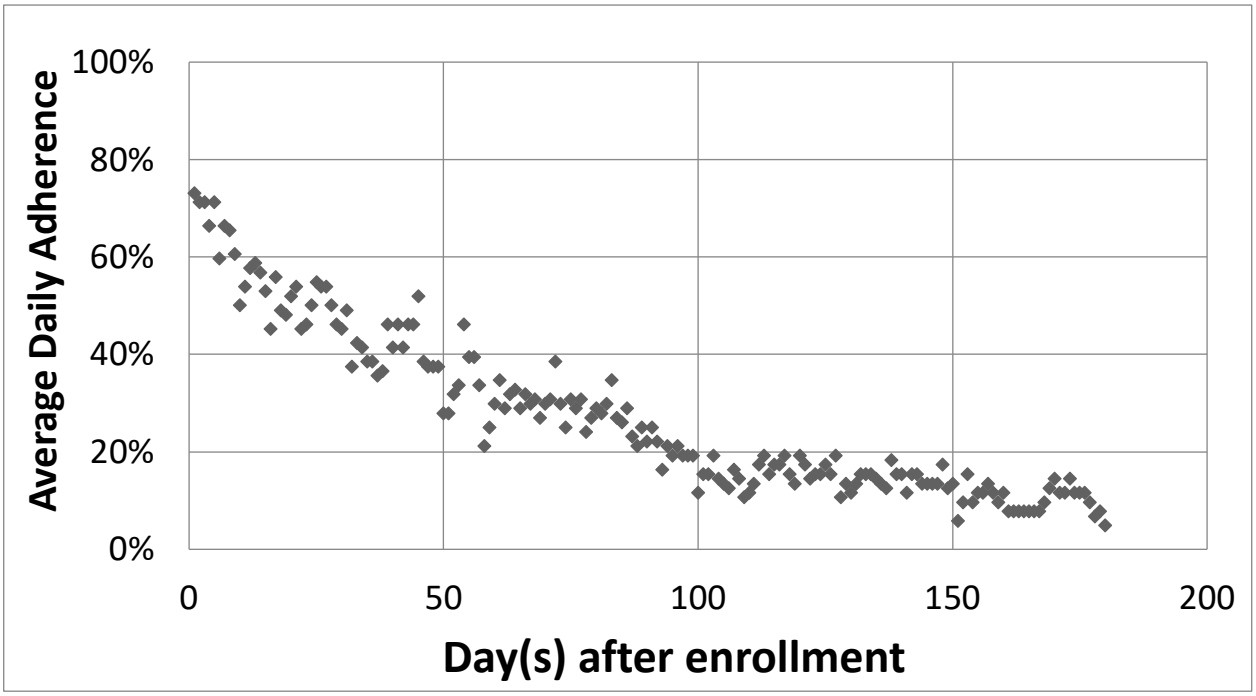

Figure 4. Average daily adherence based on EMD.

	Intervention (N=29)	Control (N=12)	Chi-square test
Baseline AMR (N, %)			
< 50%	12 (41%)	6 (50%)	0.73
>= 50%	17 (59%)	6 (50%)	
6 – month AMR (N, %)			
< 50%	10 (35%)	4 (33%)	1.0
>= 50%	19 (65%)	8 (67%)	

Table 6. Asthma Medication Ratio (AMR).

Device Performance and Patient Acceptability

Out of the 21 participants in the intervention group who received follow-up visits, one participant never utilized the EMD due to changes in medication therapy. Out of the 20 participants who utilized the EMD, 13 (65%) participants experienced technical issues. Seven out of the 13 participants experienced technical issues related to syncing problems between the EMD and the BreatheSmart app.

Out of the 29 participants in the intervention group, 16 participants completed the 5-item questionnaire on patient acceptability of the intervention at their 6-month follow up visit. Table 7 summarizes results from this questionnaire. Patient satisfaction with the intervention was high, with high median scores for Questions 1 and 4 (median scores = 5 and 4, respectively). Perceived control of asthma symptoms (Questions 2 and 3) also had relatively high scores (median score = 4 for both), although the mean was less than 4 for Question 2. Lastly, patient acceptability of physician feedback was also high (median score = 4).

Question	N	Mean (SD)	Median (Q1, Q3)
1) I would be happy to continue using my BreatheSmart app and HeroTracker	15	4.5 (0.7)	5.0 (4.0, 5.0)
2) I feel more control of my asthma now	15	3.9 (1.1)	4.0 (3.0, 5.0)
3) Knowing when to take my asthma medication is easy	15	4.1 (1.0)	4.0 (3.0, 5.0)
4) I would recommend using this to other people I know with asthma	15	4.3 (0.8)	4.0 (4.0, 5.0)
5) Going over how often I take my asthma medication with my doctor was helpful	16	4.0 (1.1)	4.0 (3.8, 5.0)

Table 7. Patient acceptability of intervention.

DISCUSSION:

In this preliminary analysis of data from a part of a larger randomized, controlled trial, we did not see any significant differences in adherence rates between the control and intervention groups after six months. Additionally, there was no statistically significant change in adherence between the control and intervention group. Interestingly, adherence rates for both groups fell from baseline to 6 – months. Additionally, we did not demonstrate any significant changes in AMR, a measure of asthma control, within the intervention group. From our data obtained from EMDs, while we did see an initial high rate of adherence within the first seven days of intervention, this rate was not sustainable after 180 days.

Multiple factors may have contributed to the decrease in adherence for both groups. Both groups lacked adequate clinical follow-up. The majority of the participants in both the control and intervention groups did not have a follow-up at three and six months after enrollment. Since

our follow-up visits are meant to align with regularly scheduled clinic visits, this meant that the majority of children in both groups did not receive clinically-indicated follow up visits to adequately monitor their asthma control. For the intervention group in particular, this meant that 55% of participants did not receive physician feedback on adherence, a vital part of our intervention (Figure 2). Additionally, asthma is a highly seasonal disease. Most asthma patients are highly symptomatic during school months (September to June). Due to the timeline of this study, the majority of participants were enrolled prior to June 2018. This means baseline adherence was assessed over more symptomatic months, while the majority of intervention months occurred over less symptomatic summer months. During this time, children may be less adherent due to decreased symptoms and may be less likely to attend clinical follow-up visits due to inconsistent schedules during the summer months. This decrease in adherence over time for the control group is consistent with results from previous adherence interventional studies that have also monitored asthmatic children over study periods of six months (Morton et al, 2017; Charles et al, 2007).

Within the intervention group, we did not see any significant, sustainable improvements in adherence. While other studies have demonstrated increased adherence rates for intervention groups, many had continual monitoring of participants with prompt interventions (e.g. calling, text-messaging) when there were recordings of non-adherence registered from the EMDs. Since we wanted to assess whether this technology would be adaptable to this high-risk pediatric population, lack of close monitoring could be one of the explanations for the statistically significant fall in adherence after the initial seven to 30 days after enrollment. Technical difficulties could also have contributed to the lack of change with intervention. The high rate of technical difficulties (65%) amongst the intervention group indicates that this could have been a

barrier for implementation of technology. In particular, syncing issues seemed to have been a major part of the reason why these technical issues occurred. Though the tracker is supposed to store any doses that were actuated but not synced with the phone, it is unclear if any doses may have been missed due to syncing issues. Additionally, the concept of "app fatigue" is evidenced by the increase in usage of mobile phone apps across all age-groups (Zhao et al, 2016). Despite this, a study showed that 25% of people will abandon an app after one use, and 62% of users will use an app less than 11 times (Perez, 2016). For an intervention where efficacy is highly dependent on sustainable usage of the phone app, this could have been a major limiting factor for sustainable usage of the intervention, as evidenced by the steep drop in average daily adherence after the first week. Lastly, while physician feedback was meant to be individualized in nature in order to address both intentional as well as non-intentional barriers to adherence, it was impossible to monitor for consistencies in the quality of feedback that participants received at their follow-up appointments. We did not assess for variability in clinician approach to interpreting adherence data on the CoheroConnect dashboard along with the role that adherence feedback played in clinical decision-making, which made standardization of clinician feedback difficult. These factors could have all contributed to the lack of sustainable rates of adherence in this intervention group.

One of the key aspects of this study was to assess for the feasibility of implementing this intervention in the clinical setting. As evidenced by the high variability in the adherence results using different modes of assessing for adherence in this study (e.g. questionnaire format using TAI, pharmacy refill data calculated as PDC, self-report, and adherence based on EMD), lack of consistent and accurate means of measuring adherence can hinder clinical decision making for physicians. At baseline, self-reported rates of adherence were consistently high (>80%), yet rates

obtained using pharmacy refill data showed adherence rates were on average less than 50%. This is consistent with published rates of asthma adherence in children (Sherman et al, 2000; Otsuki et al, 2009). While we cannot compare EMD adherence rates at baseline, the average EMD adherence rate at the end of the study was much lower than the average adherence rate obtained using PDC (27.4% vs 41%). Here, our study is consistent with other studies that have also demonstrated EMD adherence rates to be lower than the rates obtained using pharmacy refill and self-report (Bender et al, 2000; Jentzsch et al, 2009). Based on our data, due to the aforementioned technical issues, it is difficult to infer whether adherence rates as measured by EMDs are more accurate than other modes of assessing adherence. However, this does show that EMDs are able to relay a level of detail on patients' health behaviors that clinicians were never able to see using the other methods of assessing adherence. For example, using EMDs, we were able to delineate between AM and PM doses. While we did not demonstrate any differences in missed doses based on timing of the doses, this shows that this technology can offer such explanation for health behaviors over time. Being able to understand patterns in health behaviors is the first step in being able to counsel and modify behaviors.

This study also demonstrates that there may be barriers to medication adherence that cannot be addressed using EMDs, especially in a high-risk, high-disease burden community. Our study participants were mostly made up of ethnic minorities of low-socioeconomic status with high asthma severity. The burden of disease in this study group was high, as indicated by the high rates of ED visits, hospitalizations, and oral steroid usage. In such a population, a multidisciplinary approach including care coordination efforts, is vital in addressing psychosocial and environmental factors (Burke et al, 2016). Factors such as parental stresses as well as childhood stress related to residence in low-income, inner-city communities negatively

influences asthma self-management, and is associated with morbidity and non-adherence (Butz et al, 2014). Additionally, as evidenced by our low return rate for follow-up visits, there may be additional issues related to access to care that could not have been addressed in this study. These factors are vital aspects of preventive care, especially in inner-city children with asthma (Butz et al, 2014). While EMDs may be able to address intentional non-adherence, and feedback may be able to tackle some aspects of non-intentional non-adherence, without consistent care coordination efforts, we cannot effectively address environmental factors that greatly influence asthma severity and disease burden. Additionally, there are practical considerations when addressing socioeconomic factors in the clinical setting. With increasing time restraints put on clinicians, it is increasingly difficult to effectively address both medical as well as social issues that patients may face. While the pulmonary clinic at Connecticut Children's Medical Center is a specialty clinic, there are no consistent care coordination efforts in the form of care coordinators given to every child with asthma, limiting the resources that patients have access to. This, along with time limitations, could have greatly influenced the quality of feedback that participants received.

Overall, despite lack of change in adherence seen in the intervention group, we saw that patient acceptability of the intervention was high after six months of use. Participants reported willingness to continue use as well as recommending use to others. Additionally, participants reported perceived control of asthma symptoms, and responded favorably to physician feedback. Of course, similar to other studies, our acceptability questionnaire was not validated (Chan et al, 2016; Foster et al, 2012). We did not control for whether participants or parents answered the questionnaire. If the parent answered, it is uncertain the response was from the person who managed the participant's asthma care. For participants, young children could have had difficulty

comprehending the language used in the questionnaires, and older children could have refused to complete questionnaires or provided inaccurate answers. Thus, further validation testing of the questions in this questionnaire would be needed.

Several other limitations existed for this study. First, we did not have a study arm that only had EMDs with no phone app or feedback intervention. This made it difficult to compare EMD data between control and intervention groups. Additionally, we did not have a period of time with the EMD to accurately measure baseline adherence. Thus, our only way of measuring adherence that was consistent between groups was based on pharmacy refill data, which has been shown to be less accurate than EMDs (Jentzsch et al, 2009). Additionally, we did not control for who the app was given to, only that the app was given to whomever managed the child's asthma at home. Thus, the intervention was not given to consistently address self-management of asthma, which means other parental factors could have influenced usage of the EMD and app. Another limitation to the study was the fact that we could not analyze any of the rescue data from the rescue EMD given to participants. We found that very few participants recorded any rescue inhaler use, which was the reason this data was not included for analysis. This was unlikely due to lack of rescue inhaler use, as evidenced by the poorly controlled asthma in our participants. This could be due to the fact many patients have multiple rescue inhalers – one for home, one for school - meaning we could not fully capture the full extent of use with only one tracker given to participants. Lastly, as this analysis was preliminary, the study cohort analyzed represents only a portion of all the participants in the trial. Further follow-up and recruitment would likely account for the seasonality of disease mentioned previously, as well as a better understanding of how this intervention could affect pediatric asthma.

CONCLUSION:

In conclusion, this is the first study to our knowledge that looks at the feasibility as well as acceptability of using EMDs along with clinician feedback in a high-risk, high disease-burden community like Hartford, Connecticut. Our preliminary data did not show any significant changes to adherence after implementation of this intervention in children with persistent asthma. However, patient acceptability of EMDs was high despite technical issues related to the device which still needs to be resolved prior to use in the clinical setting. Overall, this study reinforces the fact that non-adherence to asthma controller medications in children remains suboptimal, especially in low-socioeconomic communities. Significant barriers to adherence still exist that may not be adequately addressed with EMDs alone, but EMDs could potentially offer greater insight into children's health behaviors. Thus, further research as well as follow-up on the rest of the cohort of participants in this study is needed in order to elucidate the role that EMDs can play in the management of asthma in children and adolescents.

REFERENCES:

Akinbami, L. J., Moorman, J. E., Bailey, C., Zahran, H. S., King, M., Johnson, C. A., et al. (2012). Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief, (94)*(94), 1-8.

Andrews, A. L., Simpson, A. N., Basco, W. T., Jr, & Teufel, R. J.,2nd. (2013). Asthma medication ratio predicts emergency department visits and hospitalizations in children with asthma. *Medicare & Medicaid Research Review, 3*(4), mmrr.003.04.a05. doi:10.5600/mmrr.003.04.a05

Apter, A. J., Wang, X., Bogen, D. K., Rand, C. S., McElligott, S., Polsky, D., et al. (2011). Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: A randomized controlled trial. *The Journal of Allergy and Clinical Immunology, 128*(3), 516-23.e1-5. doi:10.1016/j.jaci.2011.05.010 [doi]

Barnes, C. B., & Ulrik, C. S. (2015). Asthma and adherence to inhaled corticosteroids: Current status and future perspectives. *Respiratory Care, 60*(3), 455-468. doi:10.4187/respcare.03200 [doi]

Barnett, S. B., & Nurmagambetov, T. A. (2011). Costs of asthma in the United States: 2002-2007. *The Journal of Allergy and Clinical Immunology, 127*(1), 145-152. doi:10.1016/j.jaci.2010.10.020 [doi]

Beck, A. F., Bradley, C. L., Huang, B., Simmons, J. M., Heaton, P. C., & Kahn, R. S. (2015). The pharmacy-level asthma medication ratio and population health. *Pediatrics, 135*(6), 1009. doi:10.1542/peds.2014-3796

Bender, B., Wamboldt, F. S., O'Connor, S. L., Rand, C., Szefler, S., Milgrom, H., et al. (2000). Measurement of children's asthma medication adherence by self report, mother report, canister weight, and doser CT. *Annals of Allergy, Asthma & Immunology : Official Publication of the American College of Allergy, Asthma, & Immunology, 85*(5), 416-421.

Bender, B. G., & Rand, C. (2004). Medication non-adherence and asthma treatment cost. *Current Opinion in Allergy and Clinical Immunology, 4*(3), 191-195. doi:00130832-200406000-00009 [pii]

Bidwal, M., Lor, K., Yu, J., & Ip, E. (2017). Evaluation of asthma medication adherence rates and strategies to improve adherence in the underserved population at a federally qualified health center. *Research in Social and Administrative Pharmacy, 13*(4), 759-766. doi:https://doi.org/10.1016/j.sapharm.2016.07.007

Bonini, M., & Usmani, O. S. (2018). Novel methods for device and adherence monitoring in asthma. *Current Opinion in Pulmonary Medicine, 24*(1), 63-69. doi:10.1097/MCP.0000000000000439 [doi]

Bonini, M., & Usmani, O. S. (2018). Novel methods for device and adherence monitoring in asthma. *Current Opinion in Pulmonary Medicine, 24*(1), 63-69. doi:10.1097/MCP.0000000000000439 [doi]

Britto, M. T., Rohan, J. M., Dodds, C. M., & Byczkowski, T. L. (2017). A randomized trial of user-controlled text messaging to improve asthma outcomes: A pilot study. *Clin Pediatr (Phila), 56*(14), 1336-1344. doi:10.1177/0009922816684857

Burgess, S. W., Sly, P. D., & Devadason, S. G. (2010). Providing feedback on adherence increases use of preventive medication by asthmatic children. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma, 47*(2), 198-201. doi:10.3109/02770900903483840 [doi]

Burgess, S. W., Sly, P. D., Morawska, A., & Devadason, S. G. (2008). Assessing adherence and factors associated with adherence in young children with asthma. *Respirology (Carlton, Vic.), 13*(4), 559-563. doi:10.1111/j.1440-1843.2008.01292.x [doi]

Burgess, S., Sly, P., & Devadason, S. (2011). Adherence with preventive medication in childhood asthma. *Pulmonary Medicine,* 73849; 973849-973849. doi:10.1155/2011/973849

Burke, H., Davis, J., Evans, S., Flower, L., Tan, A., & Kurukulaaratchy, R. J. (2016). A multidisciplinary team case management approach reduces the burden of frequent asthma admissions. *ERJ Open Research, 2*(3), 00039-2016. doi:10.1183/23120541.00039-2016

Butz, A. M., Kub, J., Bellin, M. H., & Frick, K. D. (2013). Challenges in providing preventive care to inner-city children with asthma. *The Nursing Clinics of North America, 48*(2), 241-257. doi:10.1016/j.cnur.2013.01.008

CDC. (2015). *Most recent asthma data.* Retrieved from https://www.cdc.gov/asthma/most_recent_data.htm

CDC. (2016). *National hospital ambulatory medical care survey: 2014 emergency department summary tables.* Retrieved from https://www.cdc.gov/nchs/data/nhamcs/web_tables/2014_ed_web_tables.pdf

Chan, A. H., Stewart, A. W., Foster, J. M., Mitchell, E. A., Camargo, C. A.,Jr, & Harrison, J. (2016). Factors associated with medication adherence in school-aged children with asthma. *ERJ Open Research, 2*(1), 10.1183/23120541.00087-2015. eCollection 2016 Jan. doi:00087-2015 [pii]

Chan, A. H., Stewart, A. W., Harrison, J., Camargo, C. A.,Jr, Black, P. N., & Mitchell, E. A. (2015). The effect of an electronic monitoring device with audiovisual reminder function on

adherence to inhaled corticosteroids and school attendance in children with asthma: A randomised controlled trial. *The Lancet.Respiratory Medicine, 3*(3), 210-219. doi:10.1016/S2213-2600(15)00008-9 [doi]

Chan, A. H. Y., Harrison, J., Black, P. N., Mitchell, E. A., & Foster, J. M. (2015). Using electronic monitoring devices to measure inhaler adherence: A practical guide for clinicians. *The Journal of Allergy and Clinical Immunology: In Practice, 3*(3), 335-349.e5. doi:10.1016/j.jaip.2015.01.024

Chan, A. H. Y., Stewart, A. W., Harrison, J., Black, P. N., Mitchell, E. A., & Foster, J. M. (2017). Electronic adherence monitoring device performance and patient acceptability: A randomized control trial. *Expert Review of Medical Devices, 14*(5), 401-411. doi:10.1080/17434440.2017.1322505

Charles, T., Quinn, D., Weatherall, M., Aldington, S., Beasley, R., & Holt, S. (2007). An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma. *The Journal of Allergy and Clinical Immunology, 119*(4), 811-816. doi:S0091-6749(07)00006-1 [pii]

Choudhry, N. K., Shrank, W. H., Levin, R. L., Lee, J. L., Jan, S. A., Brookhart, M. A., et al. (2009). Measuring concurrent adherence to multiple related medications. *The American Journal of Managed Care, 15*(7), 457-464. doi:11316 [pii]

Choudhry, N. K., Shrank, W. H., Levin, R. L., Lee, J. L., Jan, S. A., Brookhart, M. A., et al. (2009). Measuring concurrent adherence to multiple related medications. *The American Journal of Managed Care, 15*(7), 457-464.

Chung, K. F., & Naya, I. (2000). Compliance with an oral asthma medication: A pilot study using an electronic monitoring device. *Respiratory Medicine, 94*(9), 852-858.

Collaborative for Asthma Equity in Children. (2016). *2016 Asthma Community Needs Assessment in Children in Hartford.* Retrieved from https://www.connecticutchildrens.org/wp-content/uploads/2017/03/Asthma_CHNA_2016.pdf

Cope, S. F., Ungar, W. J., & Glazier, R. H. (2008). Socioeconomic factors and asthma control in children. *Pediatric Pulmonology, 43*(8), 745-752.

Cote, I., Farris, K., & Feeny, D. (2003). Is adherence to drug treatment correlated with health-related quality of life? *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, 12*(6), 621-633.

Desai, M., & Oppenheimer, J. J. (2011). Medication adherence in the asthmatic child and adolescent. *Current Allergy and Asthma Reports, 11*(6), 454-464. doi:10.1007/s11882-011-0227-2 [doi]

Engelkes, M., Janssens, H. M., de Jongste, J. C., Sturkenboom, M. C., & Verhamme, K. M. (2015). Medication adherence and the risk of severe asthma exacerbations: A systematic review. *The European Respiratory Journal, 45*(2), 396-407. doi:10.1183/09031936.00075614 [doi]

Fedele, D. A., Cushing, C. C., Fritz, A., Amaro, C. M., & Ortega, A. (2017). Mobile health interventions for improving health outcomes in youth: A meta-analysis. *JAMA Pediatrics, 171*(5), 461-469. doi:10.1001/jamapediatrics.2017.0042

Ferrante, G., Malizia, V., Antona, R., Corsello, G., & La Grutta, S. (2013). The value of FeNO measurement in childhood asthma: Uncertainties and perspectives. *Multidisciplinary Respiratory Medicine, 8*(1), 50. doi:10.1186/2049-6958-8-50

Fleming, L. (2018). Adherence to medication in children and adolescents with asthma: Methods for monitoring and intervention *Expert Review of Clinical Immunology, 14*(12), 1055-1063. doi:10.1080/1744666X.2018.1532290

Foster, J. M., Smith, L., Usherwood, T., Sawyer, S. M., Rand, C. S., & Reddel, H. K. (2012). The reliability and patient acceptability of the SmartTrack device: A new electronic monitor and reminder device for metered dose inhalers. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma, 49*(6), 657-662. doi:10.3109/02770903.2012.684253 [doi]

Foster, J. M., Usherwood, T., Smith, L., Sawyer, S. M., Xuan, W., Rand, C. S., et al. (2014). Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *The Journal of Allergy and Clinical Immunology, 134*(6), 1260-1268.e3. doi:S0091-6749(14)00802-1 [pii]

Gillette, C., Rockich-Winston, N., Kuhn, J. A., Flesher, S., & Shepherd, M. (2016). Inhaler technique in children with asthma: A systematic review. *Academic Pediatrics, 16*(7), 605-615. doi:https://doi.org/10.1016/j.acap.2016.04.006

Gong, T., Lundholm, C., RejnÃ¶, G., Mood, C., LÃ¥ngstrÃ¶m, N., & Almqvist, C. (2014). Parental socioeconomic status, childhood asthma and medication use--a population-based study. *PloS One, 9*(9), e106579; e106579-e106579. doi:10.1371/journal.pone.0106579

Holley, S., Morris, R., Knibb, R., Latter, S., Liossi, C., Mitchell, F., et al. (2017). Barriers and facilitators to asthma self-management in adolescents: A systematic review of qualitative and quantitative studies. *Pediatric Pulmonology, 52*(4), 430-442. doi:10.1002/ppul.23556 [doi]

Iuga, A. O., & McGuire, M. J. (2014). Adherence and health care costs. *Risk Management and Healthcare Policy, 7*, 35-44. doi:10.2147/RMHP.S19801 [doi]

Jentzsch, N. S., Camargos, P. A., Colosimo, E. A., & Bousquet, J. (2009). Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. *Allergy, 64*(10), 1458-1462. doi:10.1111/j.1398-9995.2009.02037.x [doi]

Jimmy, B., & Jose, J. (2011). Patient medication adherence: Measures in daily practice. *Oman Medical Journal, 26*(3), 155-159. doi:10.5001/omj.2011.38 [doi]

Krishnan, J. A., Bender, B. G., Wamboldt, F. S., Szefler, S. J., Adkinson, N. F.,Jr, Zeiger, R. S., et al. (2012). Adherence to inhaled corticosteroids: An ancillary study of the childhood asthma management program clinical trial. *The Journal of Allergy and Clinical Immunology, 129*(1), 112-118. doi:10.1016/j.jaci.2011.10.030 [doi]

Lam, W. Y., & Fresco, P. (2015). *Medication adherence measures: An overview* Retrieved from http://dx.doi.org/10.1155/2015/217047

Lasmar, L., Camargos, P., Champs, N. S., Fonseca, M. T., Fontes, M. J., Ibiapina, C., et al. (2009). Adherence rate to inhaled corticosteroids and their impact on asthma control. *Allergy, 64*(5), 784-789. doi:10.1111/j.1398-9995.2008.01877.x [doi]

Liu, A. H., Zeiger, R., Sorkness, C., Mahr, T., Ostrom, N., Burgess, S., et al. (2007). Development and cross-sectional validation of the childhood asthma control test. *The Journal of Allergy and Clinical Immunology, 119*(4), 817-825. doi:S0091-6749(07)00167-4 [pii]

Liu, A. H., Zeiger, R., Sorkness, C., Mahr, T., Ostrom, N., Burgess, S., et al. (2007). Development and cross-sectional validation of the childhood asthma control test. *The Journal of Allergy and Clinical Immunology, 119*(4), 817-825. doi:S0091-6749(07)00167-4 [pii]

Makhinova, T., Barner, J. C., Richards, K. M., & Rascati, K. L. (2015). Asthma controller medication adherence, risk of exacerbation, and use of rescue agents among texas medicaid patients with persistent asthma. *Journal of Managed Care & Specialty Pharmacy, 21*(12), 1124-1132. doi:2015(21)12: 1124-1132 [pii]

Martin, B. C., Wiley-Exley, E., Richards, S., Domino, M. E., Carey, T. S., & Sleath, B. L. (2009). Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Ann Pharmacother, 43*(1), 36-44. doi:10.1345/aph.1K671

Mazumdar, S., Ghosh, S., & Mukherjee, S. (2015). Non-adherence to asthma medications: Relation to socio-economic status and asthma education. *Eur Respir J, 46*, OA4792. doi:10.1183/13993003.congress-2015.OA4792

McGrady, M. E., & Hommel, K. A. (2013). Medication adherence and health care utilization in pediatric chronic illness: A systematic review. *Pediatrics, 132*(4), 730-740. doi:10.1542/peds.2013-1451 [doi]

Milgrom, H., Bender, B., Ackerson, L., Bowry, P., Smith, B., & Rand, C. (1996). Noncompliance and treatment failure in children with asthma. *The Journal of Allergy and Clinical Immunology, 98*(6 Pt 1), 1051-1057. doi:S0091674996003582 [pii]

Mokoka, M. C., McDonnell, M. J., MacHale, E., Cushen, B., Boland, F., Cormican, S., et al. (2019). Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy. Results from a systematic literature review and modelling study. *Eur Respir J,* 1802161. doi:10.1183/13993003.02161-2018

Morton, R. W., Elphick, H. E., Rigby, A. S., Daw, W. J., King, D. A., Smith, L. J., et al. (2017). STAAR: A randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. *Thorax, 72*(4), 347-354. doi:10.1136/thoraxjnl-2015-208171 [doi]

Morton, R. W., Everard, M. L., & Elphick, H. E. (2014). Adherence in childhood asthma: The elephant in the room. *Archives of Disease in Childhood, 99*(10), 949-953. doi:10.1136/archdischild-2014-306243 [doi]

Morton, R. W., Elphick, H. E., Rigby, A. S., Daw, W. J., King, D. A., Smith, L. J., et al. (2017). STAAR: A randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. *Thorax, 72*(4), 347. doi:10.1136/thoraxjnl-2015-208171

Mulvaney, S. A., Ho, Y. X., Cala, C. M., Chen, Q., Nian, H., Patterson, B. L., et al. (2013). Assessing adolescent asthma symptoms and adherence using mobile phones. *Journal of Medical Internet Research, 15*(7), e141. doi:10.2196/jmir.2413 [doi]

National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. (2007). *Expert panel report 3: Guidelines for the diagnosis and management of asthma* (Guideline No. 07-4051). Bethesda, MD: National Heart, Lung, and Blood Institute.

Nepaul, A. N., Peng, J., Kloter, A., Hewes, S., & Boulay, E. (2012). *The burden of asthma in Connecticut.* Retrieved from https://portal.ct.gov/-/media/Departments-and-Agencies/DPH/dph/hems/asthma/pdf/4Summarypdf.pdf?la=en

Normansell, R., Kew, K. M., & Stovold, E. (2017). Interventions to improve adherence to inhaled steroids for asthma. *The Cochrane Database of Systematic Reviews, 4*, CD012226. doi:10.1002/14651858.CD012226.pub2 [doi]

O'Connor, S. L., Bender, B. G., Gavin-Devitt, L. A., Wamboldt, M. Z., Milgrom, H., Szefler, S., et al. (2004). Measuring adherence with the doser CT in children with asthma. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma, 41*(6), 663-670.

Onyirimba, F., Apter, A., Reisine, S., Litt, M., McCusker, C., Connors, M., et al. (2003). Direct clinician-to-patient feedback discussion of inhaled steroid use: Its effect on adherence. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology, 90*(4), 411-415. doi:S1081-1206(10)61825-X [pii]

Otsuki, M., Eakin, M. N., Rand, C. S., Butz, A. M., Hsu, V. D., Zuckerman, I. H., et al. (2009). Adherence feedback to improve asthma outcomes among inner-city children: A randomized trial. *Pediatrics, 124*(6), 1513-1521. doi:10.1542/peds.2008-2961 [doi]

Pearce, C. J., & Fleming, L. (2018). Adherence to medication in children and adolescents with asthma: Methods for monitoring and intervention. *Expert Review of Clinical Immunology, 14*(12), 1055-1063. doi:10.1080/1744666X.2018.1532290 [doi]

Pellegrino, R., Viegi, G., Brusasco, V., Crapo, R. O., Burgos, F., Casaburi, R., et al. (2005). Interpretative strategies for lung function tests. *The European Respiratory Journal, 26*(5), 948-968. doi:26/5/948 [pii]

Petrie, K. J., Perry, K., Broadbent, E., & Weinman, J. (2012). A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *British Journal of Health Psychology, 17*(1), 74-84. doi:10.1111/j.2044-8287.2011.02033.x [doi]

Plaza, V., FernÃ¡ndez-RodrÃguez, C., Melero, C., CosÃo, B.,G., Entrenas, L. M., de Llano, L. P., et al. (2016). Validation of the 'test of the adherence to inhalers' (TAI) for asthma and COPD patients. *Journal of Aerosol Medicine and Pulmonary Drug Delivery, 29*(2), 142-152. doi:10.1089/jamp.2015.1212

Pritchard, J. N., & Nicholls, C. (2015). Emerging technologies for electronic monitoring of adherence, inhaler competence, and true adherence. *Journal of Aerosol Medicine and Pulmonary Drug Delivery, 28*(2), 69-81. doi:10.1089/jamp.2014.1163 [doi]

Puranik, S., Forno, E., Bush, A., & Celedon, J. C. (2017). Predicting severe asthma exacerbations in children. *American Journal of Respiratory and Critical Care Medicine, 195*(7), 854-859. doi:10.1164/rccm.201606-1213PP [doi]

Ramsey, C. D., CeledÃ³n, J. C., Sredl, D. L., Weiss, S. T., & Cloutier, M. M. (2005). Predictors of disease severity in children with asthma in hartford, connecticut. *Pediatric Pulmonology, 39*(3), 268-275. doi:10.1002/ppul.20177

Riekert, K. A., & Rand, C. S. (2002). Electronic monitoring of medication adherence: When is high-tech best? *Journal of Clinical Psychology in Medical Settings, 9*(1), 25-34. doi:10.1023/A:1014131928789

Sherman, J., Hutson, A., Baumstein, S., & Hendeles, L. (2000). Telephoning the patient's pharmacy to assess adherence with asthma medications by measuring refill rate for

prescriptions. *The Journal of Pediatrics, 136*(4), 532-536. doi:10.1016/S0022-3476(00)90019-2

Simmons, M. S., Nides, M. A., Kleerup, E. C., Chapman, K. R., Milgrom, H., Rand, C. S., et al. (1998). Validation of the doser, a new device for monitoring metered-dose inhaler use. *Journal of Allergy and Clinical Immunology, 102*(3), 409-413. doi:10.1016/S0091-6749(98)70128-9

Spaulding, S. A., Devine, K. A., Duncan, C. L., Wilson, N. W., & Hogan, M. B. (2012). Electronic monitoring and feedback to improve adherence in pediatric asthma. *Journal of Pediatric Psychology, 37*(1), 64-74. doi:10.1093/jpepsy/jsr059 [doi]

Sumino, K., & Cabana, M. D. (2013). Medication adherence in asthma patients. *Current Opinion in Pulmonary Medicine, 19*(1), 49-53. doi:10.1097/MCP.0b013e32835b117a [doi]

Van Gaalen, J. L., Hashimoto, S., & Sont, J. K. (2012). Telemanagement in asthma: An innovative and effective approach. *Current Opinion in Allergy and Clinical Immunology, 12*(3), 235-240. doi:10.1097/ACI.0b013e3283533700 [doi]

Vasbinder, E. C., Goossens, L. M., Rutten-van Molken, M. P., de Winter, B. C., van Dijk, L., Vulto, A. G., et al. (2016). e-monitoring of asthma therapy to improve compliance in children (e-MATIC): A randomised controlled trial. *The European Respiratory Journal, 48*(3), 758-767. doi:10.1183/13993003.01698-2015 [doi]

Weinstein, A. G. (2013). Asthma adherence management for the clinician. *The Journal of Allergy and Clinical Immunology.in Practice, 1*(2), 123-128. doi:10.1016/j.jaip.2013.01.009 [doi]

Williams, L. K., Peterson, E. L., Wells, K., Ahmedani, B. K., Kumar, R., Burchard, E. G., et al. (2011). Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *The Journal of Allergy and Clinical Immunology, 128*(6), 1185-1191.e2. doi:10.1016/j.jaci.2011.09.011 [doi]

Zhao, J., Freeman, B., & Li, M. (2016). Can mobile phone apps influence people's health behavior change? An evidence review. *Journal of Medical Internet Research, 18*(11), e287; e287-e287. doi:10.2196/jmir.5692