Contemporary Clinical Trials Communications 21 (2021) 100706

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

Design, methods, and baseline characteristics of a pilot, randomized, controlled trial of the effects of an electronic monitoring device on medication adherence in children with asthma

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ARTICLE INFO

Keywords:
Asthma
Mobile health
Electronic monitoring device
Adherence
Children

ABSTRACT

Non-adherence to medication is common: Current methods of assessing adherence are inaccurate. Electronic monitoring devices (EMDs) may more accurately assess adherence, but are not currently used in practice. The design, methods, and participant baseline characteristics are described for a pilot trial of the effects of an EMD on asthma medication adherence in a pediatric population.

This was a pilot, randomized, controlled trial of children with persistent asthma managed with daily inhaled corticosteroids (ICS). Seventy-five children were randomized 2:1 to receive either two EMDs (one for ICS and one for rescue) linked via Bluetooth to a mobile application (app) or standard of care (controls). EMDs recorded dates and times of inhaler actuations and the app sent daily medication reminders to participants. Controls were provided standard care. Medication adherence was measured using pharmacy refill records and self-report, whereas EMD data were used to measure adherence in the intervention group. Secondary outcomes included asthma control, pulmonary function, and quality of life.

Results: One hundred sixty children were screened for eligibility, with 123 individuals excluded. Seventy-five children were enrolled, with 25 allocated to the control group and 50 to the intervention. The mean age of participants is 12 years old (±2.9), with equal proportions of male and female children; 45% are Latinx and 19% African-American; 77% report Medicaid or CHIP coverage. Half of participants have moderate persistent asthma and 48% had marginally controlled asthma at time of enrollment. There were no significant inter-group differences in baseline sociodemographic characteristics.

Conclusion: This pilot successfully reached target populations and met recruitment and enrollment goals. It is addressing an important knowledge gap by evaluating the effects of an EMD with a mobile app on adherence rates, findings which could prove useful in determining whether routine use of EMDs in clinical practice help children achieve better asthma control and outcomes.

Clinical Trials.gov: NCT03734861.

1. Introduction

Asthma is the most common chronic disease in children, affecting more than 6.1 million children in the US, and resulting in over 80,000 hospitalizations and 500,000 emergency department (ED) visits in 2016 [1]. Non-adherence to asthma medication is a common problem in patients with asthma, especially children, leading to more frequent asthma exacerbations, ED visits, and hospital admissions [2]. Although adherence rates of at least 75%–80% are required for adequate asthma control, adherence is often <50% [3–6].

Medication non-adherence is multifactorial, with contributing factors including lack of patient knowledge about asthma, poor under-

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https://doi.org/10.1016/j.conctc.2021.100706
Received 9 June 2020; Received in revised form 11 November 2020; Accepted 1 January 2021
Available online 6 February 2021

standing of the benefits of medication, forgetfulness, cost, lack of symptom perception, and negative attitudes toward asthma [7]. Thus, a multifactorial approach to addressing adherence is necessary. Current methods of assessing adherence, however, can be unreliable. Self-report may overestimate actual adherence [8–10] and pharmacy refill records cannot provide information about whether or not the medication was actually taken or taken appropriately [11]. Other quantitative methods, such as weighing canisters, dose counters on inhalers, and calculating medication possession ratio (MPR) using prescription refill data have all been studied as more objective ways of monitoring adherence. The reported adherence from each method, however, varies greatly, and none can accurately measure true medication use [10,12–14].

Recent studies indicate that reminder text-messages combined with medication-use tracking in patients with asthma can improve adherence by 10–52% [15–22]. Although promising, these interventions deploy audiovisual reminder systems that rely on access to the inhaler, or are based on short message services (SMS). These text-based interventions are limited in their ability to motivate participants to improve disease self-management and self-monitoring, compared with more comprehensive approaches [23], such as digital-health tools combining electronic monitoring devices (EMDs), mobile applications (apps), and provider tracking and feedback.

EMDs can be a more accurate method of assessing adherence, but are not currently routinely used in clinical practice [24]. Although EMDs have been shown to provide more accurate adherence assessment, there is a lack of research on health outcomes [10,24–26]. In addition, most prior studies had small sample sizes, short clinical follow-up, and a lack of focus on children/adolescents [27]. Therefore, more research is needed on the efficacy of EMDs in pediatric asthma management and how best to integrate EMDs into routine clinical care.

Certain barriers to asthma-medication adherence can be addressed by combining mobile-based reminders with clinician feedback informed by adherence data from EMDs. Mobile apps allow for sustained patient engagement and have been successfully implemented in other diseases to improve medication adherence and outcomes [23]. Additionally, the ability of EMDs to relay adherence data directly to clinicians, either via a patient portal or into the electronic health record (EHR), provides an opportunity to direct care-coordination efforts and resources towards those participants most in need, and provides information that could be used for point-of-care treatment decision-making. Herein we describe the design, methods, and participant baseline characteristics for a pilot trial of the effects of an EMD with mobile reminder system on asthma medication adherence in an urban pediatric population.

2. Methods

2.1. Study aims

The primary study aim was to examine the effects of an EMD and mobile app with feedback on children's medication adherence. Secondary aims were to measure the extent to which the EMD and mobile app improved the following in comparison with controls: 1) asthma control, as measured by the childhood Asthma Control Test (cACT) or Asthma Control Test™ (ACT), 2) forced expiratory volume in 1 s (FEV1), FEV1/forced vital capacity (FVC) ratio, forced expiratory flow (FEF) at 25–75% of FVC (FEF25-75), and exhaled fraction of nitric oxide (FeNO), 3) quality of life, as measured by the Asthma Pediatric Quality of Life Inventory™ (PedsQL), 4) frequency of asthma exacerbations (including number of acute-care visits, ED visits, hospitalizations, and courses of acute systemic corticosteroid therapy), and 5) number of self-reported missed school days.

2.2. Study population

The study population consisted of children with persistent asthma seeking care at Connecticut Children's Medical Center (CCMC) pulmonary or primary-care clinics. This is an ideal setting for the proposed study because these pulmonary and primary-care clinics serve more than 1400 children with persistent asthma per year.

2.3. Eligibility criteria

Children were eligible for the study if they met inclusion criteria (Table 1).

2.4. Recruitment sites and process

Potentially eligible participants were identified from the CCMC pulmonary and primary-care clinics' daily schedule (based on age, diagnosis, and medication list). Potential participants were only approached if they met the following initial inclusion criteria: 8–17 years old, documented diagnosis of persistent asthma, and prescription of a daily ICS. Once these criteria were confirmed, research personnel approached the patient and caregiver to determine interest in the study and administer the screening questionnaire to confirm that the child met all inclusion criteria (Table 1). Children also could be referred to this study by their pulmonary or primary-care provider.

2.5. Study protocol

Parents and children interested in study participation first signed a detailed written consent form approved by the CCMC Institutional Review Board. Interested parents/guardians and children then completed a brief, orally administered screening questionnaire (in English or Spanish, according to parental preference) to confirm eligibility, determine baseline characteristics, and record contact information.

For children who were eligible and wished to participate, research staff then opened a sealed randomization envelope (see Randomization section below), and informed the parent and child whether the child had been assigned to the intervention or control group. Participants enrolled in the intervention received the HeroTracker EMD and BreatheSmart app (see Intervention section below). Participants assigned to the control group received no additional interventions. Participants enrolled in both groups were given a $35 gift card after the six-month follow-up visit. Participants who declined participation in the study at any

Table 1
Inclusion and exclusion criteria for participation in a pilot, randomized, controlled trial of the effects of an electronic monitoring device on medication adherence in children with asthma.

Inclusion Criteria	Exclusion Criteria
• Age: 8–17 years old • Diagnosis of persistent asthma for at least six months • Prescribed daily inhaled corticosteroid (ICS) for at least one month prior to enrollment • Use of a pressurized metered dose inhaler (pMDI) or diskus compatible with Cohero HeroTracker • Parent/child possess compatible smartphone (iOS 8.0 or higher or Android) • English or Spanish proficient	• Presence of another chronic lung disease or condition, including: - Cystic fibrosis - Interstitial lung disease - Chronic lung disease of prematurity - Recurrent aspiration - Presence of tracheostomy • Presence of other chronic medical condition, such as congenital heart disease or immunodeficiency • Presence of other comorbidities that interfere with study procedures or limit life expectancy to < 1 year • Currently pregnant or planning to become pregnant during the trial period

point in the recruitment process were noted along with their refusal reasons.

2.6. Randomization

Subjects were allocated using a computer-generated, stratified randomization process. Stratified randomization ensures that compared maneuvers in an RCT are suitably distributed among pertinent subgroups [28]. The pertinent subgroups in this study were the two age groups: 8–12 and 13–17 years old, based on the PedsQL™ short module.

The randomization schedule was prepared using computer-generated random numbers. Sealed Envelope Ltd. 2017 was employed to produce a blocked randomization list [29]. Sequentially numbered, opaque, sealed envelopes were produced for each age group, to ensure adequate allocation concealment. Research staff, who did not partake in any aspect of preparation of randomization schedules, opened the envelopes in the presence of enrolled participants to inform them of their group assignment. Blinding of participants and research staff was not possible, as the intervention group received EMDs, whereas the control participants did not.

2.7. Intervention

The EMD interface combines three technologies that allow patients, parents, and providers to monitor medication adherence: 1) HeroTracker, a wireless Bluetooth-enabled sensor that tracks inhaler actuations (Fig. 1). HeroTracker is designed for both controller and rescue medications in diskus and metered-dose-inhaler (MDI) formats, and is compatible with medications shown in Table 2; 2) BreatheSmart is a mobile app designed for use with iOS and Android mobile phone operating systems. Using Bluetooth technology, BreatheSmart synchronizes with the HeroTracker to collect medication adherence data; and 3) The CoheroConnect provider portal is a HIPAA-compliant, cloud-based program that provides real-time, actionable data to aid clinicians in managing patients with asthma. At study enrollment, controller and rescue asthma medications from the participant's asthma treatment plan were entered into the BreatheSmart app. Participants received push notifications as reminders to take their daily medications, typically prescribed once or twice daily. Participants were able to track and review their medication adherence using the app. Although only inhaler actuations are captured by HeroTracker, oral medications, such as leukotriene-receptor antagonists, can be listed in BreatheSmart and manually tracked.

Fig. 1. HeroTracker EMDs attached to rescue (left) and controller (right) inhalers.

Table 2
Asthma controller medications compatible with the BreatheSmart HeroTracker.

Daily Control	
Advair Diskus (100/50 mg), (250/50 mcg), (500/50 mcg)	Dulera 100/5 mcg and 200/5 mcg
Advair HFA (45/21 mcg), (115/21 mcg), (230/21 mcg)	Asmanex HFA
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
Symbicort 80/4.5 mcg, 160/4.5 mcg, 400/12 mcg	QVAR 40 mcg, 80 mcg
Rescue	
Atrovent HFA	
ProAir HFA	
Proventil HFA	
Ventolin HFA 60 count, 200 count	
Xopenex HFA 80 count, 200 count	

Participants were given two HeroTracker sensors, one for the controller (ICS) and another for rescue (albuterol) MDIs, allowing the app to track actuation for both types of inhalers. At the initial enrollment visit, research staff trained the participant and/or caregiver (whoever was managing the participant's daily ICS) on how to use the BreatheSmart app. Participants downloaded the app during the enrollment visit and received instruction on how to synchronize the HeroTrackers to their phone. If participants were unable to do this in the office (i.e., did not have time, their phone with them, prescribed inhalers in-hand, etc.), study personnel contacted participants after the visit to ensure participants had no issues with the installation process. During the onboarding process, study personnel helped participants enter the controller medication dosing schedule into the BreatheSmart app. Cohero terms the time windows around a scheduled dose an “interval,” and every controller-medication dose captured via the HeroTracker is allotted to a specific scheduled interval based on when it is dosed. Thus, if a participant has a schedule with two doses at 9 a.m. and two doses at 9 p.m. of a prescribed ICS, they would have two intervals that day with two doses per interval. Adherence is calculated as the proportion of daily doses taken divided by the number that they were scheduled to take.

All participants in both groups were seen at 90 and 180 days post randomization, when assessments of asthma control and medication adherence were recorded. At the 180-day visit, in appreciation of their time and effort, participants received a $35 gift card for study completion and for those in the intervention group, return of their HeroTracker. At each follow-up visit, medication changes, number of missed school days, number of adverse events, and asthma exacerbations were obtained via patient report and confirmed through chart review. Participant pulmonary function data, including FEV1, FEV1/FVC ratio, and FeNO, were obtained after the clinic visit. Asthma control and adherence were assessed using the cACT/ACT, PedsQL, and Test of Adherence to Inhalers (TAI). Prescription refill data since the last clinic visit were obtained from the pharmacy by study personnel.

At follow-up visits, the research assistant provided a print-out summary of the participant's adherence to the provider caring for the patient. The provider then reviewed these data with the patient and parent/caregiver. Adherence data for controls were obtained through pharmacy-record refill information and self-report (TAI completion). For participants unable to complete the follow-up visit at their routinely scheduled appointment, the research staff either mails, text-messages a link, or e-mails a link of the follow-up surveys to participants. Participants are reminded three times via text messages, e-mail, or phone to complete follow-up questionnaires. When there was no routine follow-up visit, pulmonary function data could not be collected.

In between visits, participants who lost devices were instructed to contact the study coordinator to obtain new devices. For medication changes between study visits, study personnel documented the change, and if the new medication was compatible with the HeroTracker, instructed participants to switch the sensor to the new inhaler.

2.8. Control group

Participants randomized to the control group continue to receive their routine clinical care. They are reminded to adhere to the prescribed therapy during their clinical encounters and when the family calls to report an illness.

2.9. Outcome measures

All participants completed surveys at baseline to collect provider-determined asthma severity, control, and medication adherence. At baseline, participants also report concomitant medications, number of missed school days in the past month and year, and asthma exacerbations requiring at least one of the following: 1) course of oral steroids, 2) doctor visits outside of standard care, 3) ED visits, and 4) hospitalizations. These episodes were verified through chart review. Participant pulmonary function data included: FEV1, FEV1/FVC ratio, and FeNO. Asthma control was assessed using the cACT or ACT [30]; quality of life was assessed with the PedsQL asthma module (both the patient and parent report) [31]; and self-reported adherence was assessed with the TAI [32]. Pharmacy refill data for asthma prescriptions during the previous six months were obtained by study personnel via phone calls with the participant's pharmacy. Because research staff were aware of participant allocation, neither data collection nor outcome assessment was blinded.

The primary study outcome was medication adherence, as measured by pharmacy refills. This was the most reliable means of measuring adherence available for both the control and intervention groups (i.e., the control group did not have EMD adherence data). Medication adherence as measured by pharmacy refills was calculated using proportion of days covered (PDC), a validated method of calculating adherence, defined as a ratio of the sum of unique days supplied based on refills over the total number of days in the assessed period [33]. PDC has been shown to be the most accurate method of assessing adherence with pharmacy refill data, compared with the medication possession ratio (MPR), using the same pharmacy refill data [34]. For baseline adherence, PDC was assessed over a six-month period prior to the enrollment date. The follow-up PDC was calculated over the six-month period from the date of enrollment. Change in PDC was calculated as the difference between the follow-up and baseline PDC.

Mean EMD adherence is calculated using the grand mean of all mean EMD daily adherence rates. This is calculated for the intervention group only, and compared with the intervention-group PDC to evaluate any difference in adherence assessment methods. Asthma Medication Ratio (AMR), a National Committee for Quality Assurance measurement for patients with persistent asthma, was also calculated [35]. Using pharmacy refill data, AMR is calculated as the ratio of the number controller refills over the sum of controller refills plus 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 [35–37]. Other secondary outcomes include cACT/ACT score, PFTs, TAI, ED visits, hospitalizations, and episodes of oral steroid use.

2.10. Analyses

2.10.1. Power and sample size

The sample size was limited by the supply of HeroTracker devices made available to us for this study ($n = 50$). As this is a pilot randomized trial, the study findings address feasibility, acceptability, and field-testing of outcomes, and will inform a future, larger randomized controlled trial, so power and sample size are not relevant [38,39].

2.10.2. Analytical methods, potential confounding, attrition, and quality control

The following analytic methods are used to evaluate the main study questions and address potential confounding, attrition, missing data, and quality-control issues:

1. The statistician and research assistant performed data entry, coding, and cleaning. Univariate analyses were performed to identify missing values, attrition, and outliers. Missing values were handled using relative imputing methods, such as listwise and pairwise deletion, mean substitution, raw maximum likelihood, and multiple imputation (depending on the missing value pattern). Attrition is defined as dropping out of the study or loss to follow-up. The goal was to use a published retention strategic framework to minimize attrition, with an aim to maintain an attrition rate below the 40% level that has been reported for community-based trials of underserved children in asthma [40].
2. Baseline sociodemographic characteristics for the two study groups were compared to ensure equivalency. Percentages were used for categorical data, and means (with standard deviations) and medians (with ranges) for continuous data. The *t*-test and Wilcoxon rank-sum test were used to examine differences between the control and intervention groups in the continuous characteristics. The Pearson's $\chi 2$ test was used to test the difference in categorical outcomes. Two-tailed *P* values are reported, with a $P < .05$ considered to be statistically significant.
3. Bivariate and correlation analyses were used to identify potential independent variables for use in multivariable analyses. Known and potential moderators of a child's adherence rate (race/ethnicity, insurance status, seasonality, and asthma severity) were examined in relation to group assignment (intervention vs. control) and outcome measures. Bivariate analyses were also conducted to evaluate the associations between group assignment and outcomes. Pearson's $\chi 2$ test, *t*-test, ANOVA, and nonparametric Wilcoxon rank-sum test were performed for bivariate analyses. Child and parental asthma-related quality of life were analyzed by coding the five-point Likert scale results, both as a categorical variable (using the $\chi 2$ test) and continuous variable (using the *t*-test).

3. Results

Recruitment occurred from January 1, 2018, until January 13, 2020. A total of 160 potential participants were screened for study eligibility (Fig. 2). Exclusions occurred for 123 candidates, because of failure to meet inclusion criteria, phone incompatibility, or the participant not being interested. The final number of subjects who fulfilled eligibility criteria and were randomized was 75, with allocation of 25 to the control group and 50 to the intervention. The final participant will complete the final six-month follow-up assessment in June 2020; therefore, the study is ongoing.

The mean age of the sample of 75 children currently enrolled in the CoHero trial is 12 years old, ranging from 8 to 17 years old (Table 3). There are equal proportions of male and female children; approximately half are Latinx and one-fifth African-American, and about three-quarters have Medicaid or CHIP coverage. Half of participants have moderate persistent asthma and almost half had marginally controlled asthma at the time of enrollment. There were no significant inter-group differences in baseline sociodemographic characteristics.

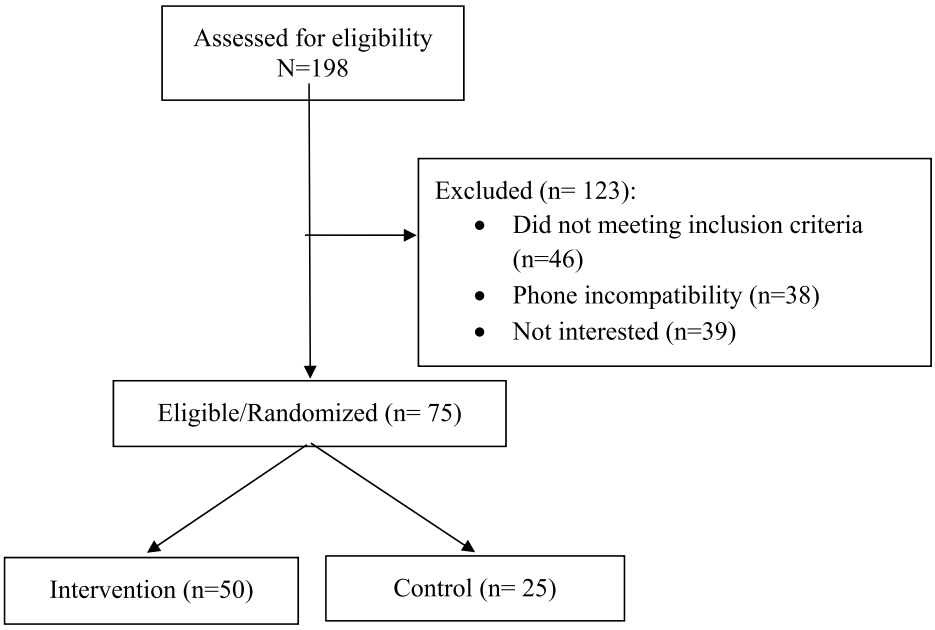

Fig. 2. Summary of participant recruitment flow, CONSORT.

Table 3
Sociodemographic characteristics of participants in the CoHero pilot trial.

Characteristic	Total (n = 75)	Control (n = 25)	Intervention (n = 50)	*P*[a]
Mean age, years (±SD)	12 (2.9)	11.7 (2.8)	12.2 (3.0)	0.34
Female	40 (53%)	14 (56%)	26 (52%)	0.11
Race/Ethnicity				
African-American	14 (19%)	6 (24%)	8 (16%)	0.28
Latinx	34 (45%)	13 (52%)	21 (42%)	
Non-Latinx white	22 (29%)	6 (24%)	16 (32%)	
Multiracial	5 (7%)	0	5 (10%)	
Public insurance	58 (77%)	21 (84%)	37 (74%)	0.95
Asthma severity				
Mild persistent	3 (4%)	1 (4%)	2 (3%)	0.45
Moderate persistent	38 (51%)	14 (56%)	24 (48%)	
Severe persistent	34 (45%)	10 (40%)	24 (48%)	
Baseline ACT score ≤19	35 (48%)	13 (52%)	22 (46%)	0.25

[a] For inter-group comparison between controls and the intervention group.

4. Discussion

The results to date document that the study design and methods have been successful in reaching the target population and meeting participant enrollment goals. The population enrolled in this pilot trial were predominantly racial/ethnic minority children covered by Medicaid or CHIP and with moderate or severe persistent asthma. The BreatheSmart interface was found to be acceptable to participants and feasible in terms of being easily attached to participants' inhalers.

The few published pilot studies regarding the feasibility of EMDs in managing asthma among children have been limited by small sample sizes and recruitment of participants from the ED or hospital after an asthma exacerbation [41–43]. In this pilot trial, we addressed a significant knowledge gap by enrolling a larger sample size and recruiting children from ambulatory clinic settings. Furthermore, we evaluated whether EMDs, combined with a reminder system and patient education, is efficacious in increasing adherence rates over a six-month period, which is longer than most studies to date.

Certain study limitations should be noted. The intervention sample size was limited by the number of EMDs provided by CoHero. In addition, EMD adherence rates cannot directly be compared between the intervention and control groups because of the study design. Furthermore, at the initiation of the study, CoHero had not designed the BreatheSmart app for compatibility with Android smartphones. Thus, a significant proportion of potentially eligible children were excluded because of Android phone ownership. Because this was a pilot study focused on feasibility and acceptability, follow-up of outcomes did not extend beyond six months."

The findings of this pilot, randomized controlled trial will be leveraged to inform a future randomized, controlled trial in a much larger sample to assess the efficacy of the interventions. Results from this study will inform future study recruitment, enrollment, and retention strategies. Furthermore, should participants in the intervention demonstrate improvements in adherence, asthma control, or lung function, the study results may be used to guide implementation of the system into clinical practice. This has the potential to decrease costs related to non-adherence-related asthma morbidity, help patients better control their symptoms, and improve quality of life.

Funding and support

There were no external funding sources used to conduct the research described here. CT Children's provided the corresponding author with institutional funds to support her time and effort and with start-up research funds to provide incentives to participants.

Declaration of competing interest

The authors have no competing interests to declare.

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