Clinical Trials Cover Page
Treatment Phenotypes for Adolescents with Asthma
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I. Hypotheses and Specific Aims:

The goal of this proposal is to better characterize medication use patterns among children with asthma and to develop provider and adolescent-focused interventions to respond to poor adherence and poor control. Asthma is the most common chronic disease in children, with a huge impact on healthcare outcomes and expenditures in the US[1]. Inhaled controller medications are the cornerstone of asthma therapy and adherence to these medications is critical to effective asthma management. However, commonly used techniques to measure adherence to daily medications are insufficiently accurate[2-6]. Reliance on patient reported measures of adherence tends to overestimate true adherence when compared to more objective measurements[6-9]. Previous evaluations of adherence using electronic monitoring devices have shown lower adherence rates to be correlated with higher levels of healthcare utilization[10], and worsened levels of asthma control[11,12]. One study found that nearly ¼ of asthma exacerbations are attributable to inhaled corticosteroid non-adherence[13]. Some estimates indicate that even achieving high adherence for 40% of children with asthma would result in cost savings of $8.2 million/year[14]. Additionally, biologic medications are now available for the treatment of refractory asthma in children, however the high cost of these medications and potential for side effects makes the objective distinction of non-adherence from treatment refractory asthma of paramount importance[15]. Medication monitoring technology allows for more accurate measures of medication adherence. Technology for monitoring adherence is expected to be widely available to providers within the next 5-10 years, and providers will need to know how to use patient adherence data to improve their patient outcomes. **Therefore, what is needed is better understanding of medication use patterns and methods of intervening to increase adherence that are feasible to implement in the clinical setting.**

Specific Aim 1) To better characterize adherence trajectory phenotypes, and to combine adherence with rescue medication use patterns to create defined asthma treatment phenotypes.

Hypothesis: we will be able to obtain distinct treatment phenotypes utilizing medication monitoring sensors.

Specific Aim 2) Use qualitative methods among adolescents and providers to evaluate reasons for adherence/nonadherence and motivating factors for adherence, feelings about device monitoring and suggested strategies for

intervention among each of the highest risk treatment phenotypes using a self-determination theory framework.

Hypothesis: Qualitative methodology will yield a number of intervention strategies that can be subjected to expert opinion

II. Background and Significance:

a. **Asthma morbidity is a significant public health problem,** with 7-9 percent of children in the US having a diagnosis of asthma in 2016, and 54% of those children having an asthma exacerbation within that year[16]. Asthma exacerbations/hospitalizations remain a significant source of healthcare expenditure[1], with an average inpatient hospitalization in children costing $3600[17], and an overall cost to the United States of $81.9 billion per year[1]. Asthma reduces productivity, resulting in approximately 14.41 million lost work days and 3.68 million lost school days per year.[18] Across the lifespan, a history of a previous exacerbation is a significant risk factor for a future exacerbation,[19,20] and has been found to be more predictive of an exacerbation than other variables including race/ethnicity and insurance status[19].

b. **Inhaled corticosteroids have been shown to significantly improve asthma control**. The use of inhaled corticosteroids (ICS) in asthmatic children and adults has been shown to significantly decrease the rate of asthma-related hospitalization[21] and asthma related death[22]. Inhaled corticosteroids have been shown in clinical trials to reduce asthma exacerbations and improve daily asthma control[23-25]. Recurrent exacerbations are also known to decrease lung function over time[26], so improving adherence to decrease exacerbations could have very important long-term implications for asthmatic children.

c. **Adherence has been correlated with improved asthma outcomes.** Previous evaluations of adherence using electronic monitoring devices have shown lower adherence rates to be correlated with higher levels of healthcare utilization[10], and worsened levels of asthma control[11,12]. One study found that nearly ¼ of asthma exacerbations are attributable to ICS non-adherence[13]. Some estimates indicate that even achieving high adherence for 40% of children with asthma would result in cost savings of $8.2 million per year[14]. For all diseases, non-adherence to medications is estimated to cost $100 billion every year in avoidable hospitalizations[27].

d. **Adherence to asthma medications is poor**[28], and even with monitoring has been shown to worsen over time [29]. The large Childhood Asthma Management Program study found that 75% of children studied had adherence levels of less than 80% when measured objectively[4]. In fact, one review of previous attempts to measure adherence to asthma medications utilizing electronic monitoring devices showed adherence rates between 28-73%, with only one study showing an adherence rate above 90% [30].

e. **There is a group of children who are highly adherent to medications but remain poorly controlled** and require escalation to biologic therapy. These therapies are expensive[31], with one model suggesting that omalizumab may cost as much as $117,000 per quality adjusted life year[15], so rapid and accurate identification of the appropriate children for this therapy is of high importance. The ability to accurately monitor adherence would permit identification of children whose poor control is related to poor adherence, potentially sparing them these extremely expensive therapies. However, there is a gap between the medications we know will work to control childhood asthma, and the behavior changes that are needed to encourage medication use.

f. **Use of theory-based approaches to behavior change** is widely recognized as key to developing interventions with demonstrated effectiveness and relevance to real-world practice [32]. Self-determination theory (SDT) is a theory of human development and motivation that has been broadly applied to health behavior change. According to SDT, human behavior is regulated along a continuum of motivation ranging from more autonomous (self-determined) to more controlled; greater environmental support for an individual's need for autonomy, competence, and belonging lead to more autonomous forms of motivation (e.g., intrinsic, integrated and identified motivation). Research consistently shows that interventions that support such needs are especially effective for enhancing the motivation and behavior of children and adolescents, including in the health domain [32]. Through application of principles and evidence-based behavior change strategies from the SDT literature, in addition to medication use monitoring, there is untapped potential for improving both initial and long-term maintenance of adherence to asthma medications.

g. **Potential Impact of the proposed study:** This study has the potential to significantly benefit children with asthma by developing the best strategies to sustain high levels of monitored adherence and identify those medication *treatment phenotypes* most in need of clinical intervention. Previous studies, including my previous work on adherence, have shown that adherence levels decline over time, even with monitoring and reminders. A better understanding of why patients follow the specific adherence trajectories that they do is key for sustained success of adherence improvement programs. Understanding adherence patterns could lead to more personalized approaches to asthma medication use, including tailored interventions addressing mechanisms that lead to poor asthma control. The issues studied here could potentially be extrapolated to many other chronic health conditions in children where adherence is also problematic.

h. **Innovation 1-Methodology: Utilizing group based trajectory modeling to place patients into adherence trajectory groupings.** Group based trajectory modeling has been utilized in evaluations of medication adherence in a number of other disease states including psoriasis[33], cystic fibrosis[34], epilepsy[35], glaucoma[36], and heart disease[37] (among others). These evaluations have shown similar adherence trajectory patterns to those seen in our pilot study, with small variations based on the number of

trajectories chosen for the models. We will extend our previous work to evaluate adherence trajectories in asthmatic children, and couple these with rescue medication use measures in order to implement treatment phenotype specific interventions, which has not previously been attempted in asthmatic children.

i. **Innovation 2-Extend the knowledge base about adherence by using mixed methods pairing qualitative data collection with objective measures of adherence.** Previously identified barriers to asthma medication adherence include lack of routine, forgetfulness and competing demands on time[38,39]. However, participants in these studies did not have objective measures of adherence to correlate with specific barriers and facilitators. The proposed study will allow for the delineation of barriers and facilitators that are particular to groups with high, low or decreasing adherence, which has not been assessed in children with asthma.

j. **Innovation 3-Programatic development that is tailored to each individual patient.** Individualized management programs have been shown to attenuate drops in medication adherence in adult asthma patients using sensor monitoring[40] and in pediatric patients using medication fills[41]. However, such programs have not yet been attempted in children using adherence monitoring.

k. **Innovation 4-Ability to accurately identify patients who are highly adherent and poorly controlled, and therefore, good candidates for expensive biologic therapies.** New, but expensive therapies such as the monoclonal antibodies omalizumab and mepolizumab are viable options for patients who have poor control but good adherence to traditional therapies. The type of monitoring technology we propose to study could allow for quicker and more accurate characterization of this patient type before they endure exacerbations potentially leading to hospitalizations and irreversible loss of lung function.

III. Preliminary Studies/Progress Report:

Pilot program to evaluate the usability and feasibility of the Propeller Health adherence monitoring device-through this work I gained skills working with this technology and population of asthmatic children

a. 25 children with high risk asthma (at least one hospitalization or 2 ED visits within the last year), monitored for 3 months.
b. Devices were well accepted by parents, children and providers, with little to no concerns from families about ease of use.
c. Average adherence rate of about 56% over the 3 month time period studied, however average adherence started at 78% and dropped to 36% by the end of the study[42].

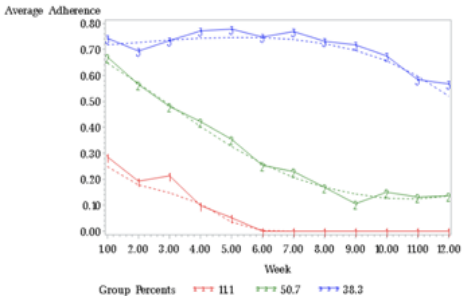


Figure 1 Adherence trajectories after 3 months of monitoring in asthmatic children (n=65)

Breathing Counts Program-through this work I gained skills of working with this technology and this population, as well as beginning to address adherence barriers

d. Adherence measured plus an asthma health educator who contacted families at regular intervals to discuss adherence and address barriers.
e. 65 patients monitored for a total of 6 months per patient
f. Has added significantly to our knowledge, by identifying likely barriers to adherence, identifying adherence trajectories after 3 months of monitoring (Fig 1), confirming that 61% of patients fell into a suboptimal adherence category, and dealing with technical support issues that might arise with the devices.

Propeller Health database evaluation-through this work I have continued to evaluate the adherence trajectories over time in a diverse population of asthmatics.

g. Initial data presented at the 2018 American Thoracic Society meeting showing stability of initial adherence trajectories over 20 weeks of monitoring in 1,234 patients. Manuscript under review

Financial Incentives for medication use

h. Evaluating the use of financial incentives for asthma medication use in asthma
i. 43/50 patients enrolled to date.

In the current proposal, I have decided to focus the evaluation on adolescents with asthma as they are a group at high risk for non-adherence, and they are often responsible for their own medication use, as opposed to younger children who depend on their parents for medication administration. I have enrolled a significant number of adolescent asthmatics in the previous two studies discussed, and I have experience in working with this age group. Additionally, I have extensive experience using the adherence monitoring devices and I am well equipped to address any technical issues that may arise.

IV. Research Methods

Specific Aim 1) To better characterize adherence trajectory phenotypes, and to combine adherence with short acting beta agonist (SABA) use patterns to create defined asthma *treatment phenotypes*.

Hypothesis: We will be able to identify distinct *treatment phenotypes* during the 12 months of monitoring.

Study Design: Longitudinal, prospective, cohort study of the medication adherence patterns of children with high risk asthma during which time they will receive adherence monitoring and notifications.

Study Setting Patients who have been seen within the last 2 years by the Pulmonary, Allergy and/or Child Health/Adolescent Medicine clinics at Children's Hospital Colorado (CHCO) Main Campus, and network-of-care sites including: Briargate, North Campus, South Campus, Parker, and CHCO in Colorado Springs. These clinics treat a variety of patients; however, a significant proportion of these patients are asthma sufferers, and the pulmonary clinic alone sees over 3000 asthma visits per year. Patients who are currently, or have been, admitted to CHCO for an asthma exacerbation may also be approached.

Study Population The study population will include children with a diagnosis of asthma, either in their "Problem List" or "Visit Diagnosis", aged 12-16 years old at the time of consent, on an inhaled controller and rescue medication that can fit the Propeller Health devices. For patients who follow the new NIH-approved SMART (single maintenance and reliever therapy) approach, their inhaled controller medication and rescue medication will

be the same. Exclusion criteria will include co-morbidities such as other significant chronic lung disease (cystic fibrosis, chronic respiratory failure, tracheostomy status, interstitial lung disease, restrictive lung disease, bronchopulmonary dysplasia, pulmonary hypertension, bronchiectasis, chronic lung disease of prematurity) on their problem list, significant developmental delay on their problem list, taking more than 3 asthma related medications (other than their quick relief medication), or primary language other than English, Spanish, Catalan, Dutch, French, German or Italian (the languages currently supported for the monitoring application), or if patients do not have a smartphone that can download the Propeller Health app. We plan to enroll 100 patients using a rolling enrollment plan over a period of 6-12 months.

Outcome Measures The primary outcome for this Specific Aim will be the medication treatment phenotype as determined by Group Based Trajectory Modeling (GBTM)[43]. We will analyze trajectories at the completion of 2, 4, 6, 8 and 12 months of monitoring for all patients in order to determine how rapidly the treatment phenotypes are established, as well as how stable they are over time.

Study Procedures We will screen for eligible participants by reviewing clinic schedules for the Pulmonary, Allergy, Child Health/Adolescent Medicine clinics, and recent admissions on a regular basis. Additionally, we may utilize EMR tools to identify all patients seen in these clinics in the past 2 years to reach out to families directly. Due to current practice changes during the COVID-19 pandemic, patients and parents will be consented either in clinic, while admitted to CHCO, or by Telehealth after a clinic visit by a member of the study team. Remote consent will be done via Vidyo on the MyChart platform, and participant ability to login to the MyChart application will be considered verification of identity for the purposes of consenting. We will use REDCap to house electronic consent documentation. If the consent occurs in person, a copy of the signed consent form will be given to the family. If the consent occurs via Telehealth, the REDCap consent responses will be emailed or mailed via USPS standard mail to the participant after the consent visit is complete. After consent is obtained and upon receipt of the Propeller Health device either in the clinic, inpatient room, or in their home, patients will be enrolled in medication use monitoring with mobile sensor technology. Participants will be given sensors to attach to their controller and rescue medications. For participants who have one medication for both their controller and rescue inhaler, they will only receive one sensor. If the consent happens in clinic or while admitted, the patients will be enrolled in the Propeller Health system at the same time. If consent occurs remotely, a second telehealth visit may be scheduled after the consent has been signed if the devices have not been received by the participant. If the patient has already received the devices, they will be enrolled in the Propeller health system immediately after consent. The sensors will sync via Bluetooth to an application on the participant's or parent's phone (or both based on participant preference) to provide feedback and reminders regarding medication adherence (push notifications will be sent if medications have not been used 15 min after the time specified by the participant on enrollment as the time they normally take their medications). Patients will be given the option to share their data with their healthcare provider, however providers will not have direct access to this data. Data will be collected regarding the exact time of inhaler actuation indicating a dose of medication being delivered. Additionally, at study entry, we will collect information regarding basic baseline demographic and clinical information (including age, medications prescribed, allergic history, lung function and secondhand smoke exposure). Participants will be given the option to receive text message reminders from the study team regarding sensor inactivity. Participants will be asked to sync their sensors to their phone application prior to disposing of the Bluetooth devices in order to remove data from the device memory. If

there are problems syncing the data, we will ask participants to mail the sensors back to the research team in order to sync the devices and obtain/remove the data.

Analytic Approach/Data Analysis Plan

Adherence trajectory modeling

Group Based Trajectory Modeling (GBTM) will be used to explore subgroups of adherence trajectories. This methodology has been previously used in medication adherence phenotyping (see innovation above), and we have previously studied this modeling technique and found good model agreement with 3 subgroup trajectories identified. We will collect data continuously and evaluate at 2, 4, 6, 8 and 12 months of monitoring for all patients, as data from the entire group is needed in order to place patients in the appropriate group trajectory. We will compare results from 2, 4, 6, 8 and 12 months of monitoring in order to determine how quickly patterns are established after the initiation of monitoring and the initial Hawthorne effect, as well as if they are stable over time. We will model average weekly adherence as a function of cubic and quadratic time and compare modeling approaches by Bayesian information criterion, Akaike information criterion, number of groups, and proportion of patients per group. For a set of trajectories to be considered reasonable, we will require that estimated group proportions remain greater than 5%. The GBTM analysis will be run in SAS software 9.4 (SAS Institute Inc, Cary, North Carolina) and the PROC TRAJ macro (http://www.andrew.cmu.edu/user/bjones/) a freely available program (Copyright (c) 2017 Bobby L. Jones). We anticipate that we will see 3 adherence trajectories based on our previous studies (high, moderate and poor adherence) (Figure 1). Additionally, we will plan to evaluate mean level of adherence over the 12 month monitoring period (>80% adherence will be considered high adherence, 30-80% will be considered moderate adherence, and less than 30% will be considered poor adherence), to compare to the GBTM modeling and provide an alternative means of assessing adherence.

Asthma Control

We will determine levels of asthma control based on NHLBI EPR-3 guidelines defining asthma impairment[44]. Asthma control will be defined on a weekly basis, with albuterol use ≤2 times per week labeled as good control, albuterol use daily labeled as poor control, and albuterol use multiple times per day labeled as very poor control. When defining a *treatment phenotype*, the poor control and very poor control groups will be combined as 'poor control'. All albuterol actuations occurring within 5 minutes will be considered a single use event. Albuterol actuations occurring outside this 5-minute window from the first actuation will be considered a separate albuterol use event. When defining a *treatment phenotype* at the end of the monitoring period, we will consider a patient to have 'poor control' if they demonstrate poor or very poor control based on the parameters above for >50% of the measured weeks of monitoring, or if they have an exacerbation requiring oral steroids during the monitoring period.

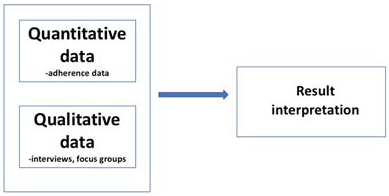
Potential Problems and Alternative Approaches

Inability to confirm adherence trajectories. The null hypothesis is that we will not be able to identify defined adherence trajectories and therefore *treatment phenotypes*. Traditional power analysis techniques do not currently exist for the group based trajectory modeling approach and this is an active field of current methodologic research. While we are reasonably confident that we will be able to successfully determine adherence trajectories based on our previous research with smaller groups of patients as well as the work in other disease states, there is a small chance that we will not be able to confirm the group based adherence trajectories. However, we will be able to evaluate medication use patterns per the other methods described above (average adherence over time). Additionally, if adolescents shift their adherence trajectories over time, we will do an in-

depth analysis to evaluate possible reasons for the change (including provider interventions and significant exacerbations).
Technical Difficulties with adherence sensors There is a risk with any technology that technical difficulties will arise that make completion of the project problematic. However, we have been working with Propeller Health for more than 3 years on 3 projects that have enrolled more than 120 patients. From this experience we have learned how to deal with sensor failures (troubleshooting along with the manufacturer, providing alternative devices) and issues with Bluetooth syncing (troubleshooting the phones, turning Bluetooth back on, alternative means of obtaining data including use of Bluetooth hubs or a provider application). We feel very confident in the technology and our ability to handle any technical support challenges that arise.

Specific Aim 2) Use qualitative methods among adolescents and providers to evaluate reasons for adherence/nonadherence and motivating factors for adherence, feelings about device monitoring and suggested strategies for intervention among each of the highest risk *treatment phenotypes* using a self-determination theory framework.
Study Setting and population: See Specific Aim 1
Study procedures: All Aim 1 participants will be considered for participation in Aim 2 qualitative analysis. Participants will range in age from 12-17 and will be recruited from Aim 1 participants. Participants who have reached age 18 prior to interview selection will not be contacted for interviews. Selected participants will be called at home to participate in a phone or remote video interview within 1 year of completing the 12-month monitoring period. A semi-structured interview guide[45] will be developed for this study by Dr. Holtrop and myself, and will be based on findings from aim 1, existing literature and expert opinion. Questions in the interview guide will explore patients' perceptions of the factors that influence medication use (including barriers and facilitators) and strategies that adolescents perceive might be helpful in improving medication adherence. Self-determination theory (SDT) will be use as a framework to provide more specific insight to factors that may influence motivation to participate in medication adherence. The most likely behavior change techniques in this case which we will explore will be 1. Implementation intentions (plans that specify the context in which a behavior will be performed), 2. Monitoring and feedback, and 3. Support for overcoming failure (i.e., contingency planning, goal revision, and enhancing recovery self-efficacy).Therefore, the interview guide will also include questions to address SDT components which include competence, relatedness and autonomy[32]. Second, clinical providers have a unique perspective on patient adherence/non-adherence issues. Providers (n=up to 30), including physicians, advanced practice providers and nurses will be grouped by role and be asked to participate in a focus group interview once during the study period. Providers will be contacted by the study team via email and asked to participate, and then scheduled based on available time. Interview questions and probes will include provider perceptions of what interventions are needed to best address patient medication use as well as the types of *treatment phenotypes* that providers think would benefit most from active intervention. To do this, we will present our proposed phenotypic groupings to the providers and ask probing questions regarding their completeness, meaning, and use in practice. The phone or video interviews will last 30-60 minutes; focus groups will last 1 hour. All will be audio recorded and transcribed verbatim.
Data analysis: To analyze the patient interview data, we will use both inductive and deductive approaches. First, using a grounded theory hermeneutic editing approach[46], the qualitative PRA and I will inductively code the interview transcripts. We will initially embark

Figure 2 Concurrent mixed methods approach



on an open coding process in which codes are developed based on reading the text. Second, using SDT as a guide, we will deductively code the data for SDT components. Next, we will use an axial coding process to determine if this theory is a good fit for the data and if additional findings emerge from a theoretical approach. Transcribed data will be entered into the Atlas.ti qualitative software analysis program (version 8; Scientific Software Development, GmbH, Berlin, Germany) and utilized for coding and analysis. We will examine the data for overall themes, SDT components, and in a matrix approach[47] by participant groups (e.g., which *treatment phenotype* the patient was in). The results generated from these processes will be used to generate a framework for evaluation of patient behavior and strategies for individualized approaches to medication adherence. The provider focus group data will be analyzed similarly as noted directly above, both separately and then together with the patient interview data. Once these data are analyzed, they will be combined with the quantitative data using a concurrent mixed methods approach[48] (figure 2), utilizing quantitative data gathered from the monitoring devices themselves, and merging that with the qualitative data obtained from the qualitative interviews and focus groups, allowing for triangulation of results across data types. Each data set will be obtained separately. Tables describing the interplay of the quantitative results in light of the qualitative results will be created.

Potential Problems and Alternative Approaches: *GBTM strategy:* As described above, there is a small chance that the patients studied may not fall into clear adherence trajectories. However, the GBTM will not affect the questions asked, nor will the interviews preclude this change in protocol. *Bias:* As Dr. Hoch is an MD pulmonary provider, there is a possibility that her patients will show evidence of desirability bias in their interactions with her. Therefore, a research assistant will conduct these interviews to minimize this bias, and she will be very clear in indicating that there will be no judgement on behaviors. *Thematic saturation:* While we expect to reach thematic saturation in the two highest risk groups by interviewing up to 50 patients, we recognize that we may not reach thematic saturation with only 30 providers. If that is the case, we will expand these focus group numbers as needed.

Participant ages: We recognize that children at the lower end of our age spectrum (age 12) may have less autonomy in medication usage than those at the upper end. Therefore we will purposefully select a broad range of ages within each *treatment phenotype* in order to capture age related differences in behavior.

Treatment effect in diverse populations-there is some evidence that diverse populations may require different cut points for markers of asthma control[52]. We plan to evaluate asthma control both by Asthma Control Test and objectively measured rescue medication use to help ameliorate this effect.

Table 2-*RE-AIM data evaluation*

G. Summarize Knowledge to be Gained:

We will be able to evaluate adolescent medication use patterns across a full year to determine medication use phenotypes. We will then be able to utilize a mixed methods approach to develop and pilot test a novel strategy to improve medication adherence in this high risk population.

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