ED-Initiated School-Based Asthma Medication Supervision (ED-SAMS) PECARN Protocol Number 038

Pediatric Emergency Care Applied Research Network
National Heart, Lung, and Blood Institute (NHLBI)

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PROTOCOL TITLE:

ED-Initiated School-Based Asthma Medication Supervision

Short Title: ED-SAMS
PECARN Protocol Number: 038

Lead Investigators and Authors:
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University of Arizona

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Contents

Nomenclature

AE: Adverse Event
CEA: Cost Effectiveness Analysis
DCC: Data Coordinating Center
DSMB: Data Safety Monitoring Board
ED: Emergency Department
ED-SAMS: ED-Initiated School-Based Asthma Medication Supervision
FDA: Food and Drug Administration
HEDA: Hospital Emergency Department Affiliates
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
ICS: Inhaled Corticosteroid
MARs: Medication Administration Record
MedDRA: Medical Dictionary for Regulatory Activities
NAEPP: National Asthma Education and Prevention Program
NHLBI: National Heart Lung and Blood Institute
PECARN: Pediatric Emergency Care Applied Research Network
PI: Principal Investigator
RA/RC: Research Assistant/Research Coordinator

Abstract

Asthma is a common chronic condition that causes substantial morbidity among children and much of it is attributable to medication non-adherence.[1, 2] The National Asthma Education and Prevention Program (NAEPP) and the American Academy of Asthma, Allergy, and Immunology have urged others to develop more effective adherence programs.[3, 4] Schools are a logical setting to deploy such interventions because they are where children congregate, spend much of their day, and are frequently monitored.[5] Because many schools serve a high proportion of minority and low-income students, engaging them presents a unique opportunity to reach populations who experience the greatest burden of preventable morbidity.

Supervising inhaled corticosteroid (ICS) use in the school setting can increase medication adherence and reduce episodes of poor asthma control.[6] Under certain conditions, it can also be cost-effective.[7] However, recruiting children from school settings tends to enroll children with mild asthma and infrequent health care use.[8] Therefore, initiating supervised treatment in these children tends to burden school personnel with unnecessary work and diminishes the program's cost-effectiveness. To address this inefficiency, we propose to recruit children who are discharged from the Hospital Emergency Departments (EDs) following successful treatment of an asthma attack. Such children have much higher risk of a future asthma attack than their peers.[9]

The Pediatric Emergency Care Applied Research Network (PECARN) comprises[10] hospital-affiliated EDs that serve 1 million acutely ill and injured children annually. Their primary research mission is to reduce childhood morbidity and mortality by establishing creative partnerships between emergency medical service providers and their surrounding communities. The networks size and geographic diversity make it uniquely situated to develop, implement, and evaluate the feasibility and effectiveness of ED-Initiated School-Based Asthma Medication Supervision (ED-SAMS).

Approximately one-third of children treated for an asthma attack within PECARN experience a second ED-managed attack within 6 months. While the NAEPP guidelines recommend that long-term ICS treatment should be initiated at ED discharge,[11] <20% of children actually receive a prescription for controller therapy.[12, 13] Observational data indicate that patients who use ICS following discharge are almost half as likely as non-users to experience a repeat ED visit.[14] Many have also argued that ED-initiated treatment could be cost-effective.[14–16] However, simply providing patients with a prescription does not ensure that they will actually use it once discharged.[10, 17–23] To ensure better medication adherence, we propose to dispense ICS at discharge and supervise its use in the school setting.[6, 7]

1 Study Summary

We intend to demonstrate that Pediatric Emergency Care Applied Research Network (PECARN) Emergency Departments (EDs) can dispense inhaled corticosteroid (ICS) and arrange its use in the school setting following successful management of an asthma attack. Furthermore, we intend to demonstrate this intervention is well-accepted by families, clinicians, and schools. Successful completion of this preliminary trial will inform the development of a larger multicenter trial to determine ED-Initiated School-Based Asthma Medication Supervision (ED-SAMS) effectiveness and cost-effectiveness among elementary-age children with mild-to-moderate asthma treated in PECARN EDs.

1.1 Hypothesis

The hypothesis of this preliminary study is that ED-SAMS will be feasible to conduct, and it will be acceptable to the providers, schools and families.

1.2 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. Determine the feasibility and acceptability of dispensing inhaled corticosteroids in the emergency department and supervising its use in the school setting.

Specific Aim 2. Estimate a range of plausible intervention effect sizes to support the development of a larger multi-center clinical trial.

Specific Aim 3. Conduct a preliminary cost-effectiveness analysis (CEA).

1.3 Primary Endpoints

The primary endpoints of this study are to:

1. Evaluate our ability to recruit 90 participants within a 6-month period,
2. Evaluate our ability to initiate supervised ICS use in the school setting within 5 business days,
3. Evaluate our ability to retain participants for the 90-day intervention period,
4. Evaluate our ability to effectively collect asthma severity data during the study period, and
5. Evaluate caregiver, school, and ED provider satisfaction with the ED-SAMS program.

1.4 Secondary Endpoint

The secondary endpoint of this study is to estimate a confidence interval of the intervention's effect size and conduct a preliminary CEA.

1.5 Subject Eligibility, Accrual and Study Duration

Eligible participants will be identified by on-site study staff.

Inclusion criteria are:

1. Children 6-12 years of age; AND
2. Treated for an asthma exacerbation as determined clinically by the principal ED provider based on symptoms such as shortness-of-breath, cough, and wheezing; AND
3. Symptoms must improve following $\geq$ 1 dose of albuterol and $\geq$ 1 dose of systemic corticosteroids such that he/she can be safely discharged home; AND
4. Must have physician-diagnosed asthma as reported by parents or documented in the electronic medical record.

Exclusion criteria are:

1. Attends a non-participating school; OR
2. Attends a participating school less than 5x/week; OR
3. Enrolled in another research study; OR
4. Patients who are hospitalized; OR
5. The patient or their consenting parent/guardian does not speak English or Spanish; OR
6. ICU admissions for asthma in the past year; OR
7. History of $\geq$ 2 hospitalizations for asthma in past year; OR
8. History of $\geq$ 2 controller medications for asthma in the past 30 days; OR
9. Study medication represents a step-down in asthma therapy in the judgement of the ED physician; OR
10. Parent does not have a cell phone; OR
11. Parent cannot send and receive text messages.

2 Introduction

2.1 Study Rationale

Asthma is a common chronic condition that causes substantial morbidity among children; much of it is attributable to medication non-adherence.[1, 2] The National Asthma Education and Prevention Program (NAEPP) and the American Academy of Asthma, Allergy, and Immunology have urged others to develop more effective adherence programs.[3, 4] Schools are a logical setting to deploy such interventions because they are where children congregate, spend much of their day, and are frequently monitored.[5] Because many schools serve a high proportion of minority and low-income students, engaging them presents a unique opportunity to reach populations who experience the greatest burden of preventable morbidity.

Supervising ICS use in the school setting can increase medication adherence and reduce episodes of poor asthma control.[6] Under certain conditions, it can also be cost-effective.[7] However, recruiting children from school settings tends to enroll children with mild asthma and infrequent health care use. Therefore, initiating supervised treatment in these children tends to burden school personnel with unnecessary work and diminishes the program's cost-effectiveness.[8] To address this inefficiency, we propose to recruit children who are discharged from the ED following successful treatment of an asthma attack. Such children have much higher risk of a future asthma attack than their peers.[9] PECARN comprises[10] hospital-affiliated EDs that serve 1 million acutely ill and injured children annually. Their primary research mission is to reduce childhood morbidity and mortality by establishing creative partnerships between emergency medical service providers and their surrounding communities. The network's size and geographic diversity make it uniquely situated to develop, implement, and evaluate the feasibility and effectiveness of ED-SAMS.

Approximately one-third of children treated for an asthma attack within PECARN experience a second ED-managed attack within 6 months. While the NAEPP guidelines recommend that long-term ICS treatment should be initiated at ED discharge,[11] <20% of children actually receive a prescription for controller therapy.[12, 13] Observational data indicate that patients who use ICS following discharge are almost half as likely as non-users to experience a repeat ED visit.[14] Many have also argued that ED-initiated treatment could be cost-effective.[14–16] However, simply providing patients with a prescription does not ensure that they will actually use it once discharged.[10, 17–23] To ensure better medication adherence, we propose to dispense ICS at discharge and supervise its use in the school setting.[6, 7]

3 Background

3.1 Significance

Approximately 8% of children in the United States have asthma. Each year, these children experience 4 million asthma attacks that result in 725,000 ED visits and 100,000 hospitalizations. Unsurprisingly, the direct medical expenditures of children with asthma are 75-90% higher than those of children without asthma. In 2016, this amount totaled 40 billion dollars. Substantial indirect costs are incurred when parents miss work to care for their children who miss school. These additional costs raise the total economic burden of asthma to $80 billion annually. Frequent asthma-related school absences impair academic achievement and social functioning. This burden falls disproportionately on minority, low-income, and urban populations. For example, black children have 60% more ED visits and 75% more hospitalizations than white children even though they have similar asthma attack rates.

Adherence to ICS is notoriously poor.[20, 22, 23] While 86% of privately insured patients who receive an ICS prescription will fill it within 30 days, only 64% will subsequently refill it again within 180 days. Even worse, only 3% will fill enough medication to cover $\geq$75% of prescribed days with average medication possession being approximately 20%. Black and Hispanic patients are 20% less likely to fill their initial prescription and are 40% less likely to refill enough medication to cover $\geq$75% of prescribed days. Adherence is similarly poor among the publicly insured. Among Medicaid-insured children, ICS is only refilled enough to cover 20% of prescribed days; fewer than 15% will fill enough to cover $\geq$50% of days.

At any given time, 40% of children with asthma are not well-controlled and much of this is attributable to nonadherence. Simulation and modeling studies suggest that maximizing ICS adherence among those prescribed ICS could reduce health care utilization by 25-45%. Even greater reductions are hypothesized if ICS prescribing could be expanded to all patients at risk of serious asthma-related exacerbations. However, a recent Cochrane review concluded that current methods of improving adherence for chronic health problems are mostly complex and not very effective. New adherence strategies will be needed if society is to achieve the gains suggested possible by simulations.

Medication non-adherence among patients with chronic disease is a multi-dimensional challenge. The cost and convenience of obtaining medication (health system factors) and the motivation needed to adhere with a daily health habit (patient-related factors) are

common barriers to adherence that are addressed by this study. Medication acquisition costs deter patients from filling and refilling prescription medications. Even small $1-3 co-payments can appreciably reduce adherence. However, imposing additional time costs by requiring more frequent refills has an even greater impact. Time costs can add $50-100 per prescription. Therefore, the $155 out-of-pocket spending estimate for children's asthma medication likely understates the true economic burden. Dispensing ICS in the ED is therefore expected to improve adherence by reducing the substantial time and travel costs associated with medication acquisition.

ICS treatment also burdens patients by requiring them to adopt a daily health habit. For children, this burden primarily falls on parents. Parents weigh the perceived benefits of treatment against their perceptions of treatment risk and burden. Given that asthma symptoms fluctuate in response to treatment and season, many purposefully reduce medication administration when their child's symptoms wane (volitional non-adherence). In the absence of treatment, the underlying inflammation is allowed to worsen and exacerbation risk increases. This reactive pattern of medication use is substantiated by the fact that 37% of all prescriptions for ICS are filled on the same day as prescriptions for oral corticosteroid, suggesting after the exacerbation, not before it.[18] Even more disturbing, less than 50% of children who filled a prescription for oral corticosteroid were ever noted to have filled an ICS prescription, meaning most lacked any access to controller medication.[18] Our proposal addresses the problem of primary non-adherence by dispensing medication in the ED and addresses non-adherence by arranging supervised use in the school setting.

4 Study Design

4.1 Study Design Overview

We propose to evaluate the feasibility and acceptability of ED-SAMS among elementary-age children with mild-to-moderate asthma who are discharged from the ED following an asthma attack. Children will be randomized to ED-dispensing with home supervision or ED-dispensing with home and school supervision. All children will be treated with a standardized medication regimen consisting of once-daily budesonide inhalation powder supplemented by as-needed albuterol sulfate.

4.2 Participant Screening and Enrollment

Research staff will approach parents of children who are being treated for symptoms consistent with an asthma attack. The research staff will explain the study and will provide parents with a brief written description. Written parental permission will be obtained from parents; assent, as applicable, will be obtained from children. Given a 6-hour turnaround between presentation and discharge within PECARN EDs, we anticipate adequate time will be available to identify, recruit, and evaluate study participants. To ensure all participants can complete 90 days of school-supervised treatment before summer break, recruitment will commence at the beginning of the school year (e.g., September) and cease in March.

To achieve our 90 participant goal, each site will be expected to enroll approximately 8 participants per month during the study enrollment windows.

4.3 Baseline Data Collection

Successful implementation of ED-SAMS will require EDs to distribute medication to schools in a timely manner and schools to administer it daily. While we are confident that schools will be willing and able to administer asthma medications at school, a number of administrative barriers must be overcome before medication administration can be initiated. For example, specific forms must be completed by parents and physicians and medication with appropriate labeling must be supplied to the school. With the support of the ED-SAMS outreach unit at the University of Arizona, ED personnel will complete all required forms prior to the child's discharge. These completed forms and the individually labeled medication will then be couriered to the school's health office within 5 business days. We expect to accomplish this for $\geq$90% of participants. With the support of the ED-SAMS outreach unit, phone contact will be made to each school's health office to ensure and document successful initiation of the first medication dose.

A variety of data will be collected from multiple sources including, but not limited to, recruitment and enrollment logs, the electronic medical record, parent and participant surveys, and school medication administration records.

4.4 Follow-up Data Collection

Parent follow-up interviews (telephone) and a text message survey will commence approximately 30 days after enrollment and will continue monthly until at least 120 days post randomization. To help ensure $\geq$67% of parent interviews are completed at the 120-day

mark, multiple calls will be attempted on home and cell-phone numbers at multiple times including nights and weekends. Parents will also be provided $40 per completed call and $1 for each text answered, a total of $10 if all texts are answered. The total compensation is $190 if all phone interviews and texts are completed. Because the notion of asthma control (or symptom reduction) remains an important outcome, we will ask parents about their child's asthma symptoms and albuterol use during each of the monthly telephone interviews and text message surveys. We will ask parents about their child's at-home medication use during the telephone interviews, as well.

An important determinant of our success will be parent and ED provider satisfaction. Parents who participated in either the "ED-dispensing with home and school supervision" or the "ED-dispensing with home supervision" arm will be asked to rate their satisfaction with the ED-SAMS program at the 120-day follow-up interview. School health personnel responsible for medication administration will be asked to complete a survey to rate their satisfaction with the ED-SAMS program. The survey will be made available near the end of the study to ensure ample time is available to make multiple solicitation attempts. ED providers will also be asked to complete a survey after the patient is discharged from the ED.

To ensure that schools are able to consistently administer ICS, we will audit the schools' medication administration records. Schools are typically required to document administration of all prescription medications.

4.5 PECARN Registry Data Review

The PECARN Registry, a continuously accruing multicenter clinical data repository of electronic health record data from seven pediatric sites, is comprised of more than 4.4 million overall pediatric ED visits and 17,000 ED visits annually for children with asthma.

The University of Arizona will send aggregate summary data from 2016 and 2019 around how many asthma patients were seen in the ED, how many patients had insurance coverage, and how many patients were on medication regimens specific to asthma. The DCC will combine these aggregate summaries with the summaries produced through PECARN Registry.

5 Study Procedures

5.1 Randomization and Enrollment

Eligible participants will be randomly assigned on a 1:1 basis to receive either guideline concordant care (ED-dispensing with home supervision) or ED-dispensing with home and school supervision. The randomization protocol will be determined by the DCC using a block permutation design to ensure balanced randomization given the small sample sizes required at each site.

Within the ED, care will be provided at the sole discretion of the primary ED provider including all tests, procedures, and treatments deemed appropriate to restore pulmonary function and safely discharge the participant home. At discharge, participants will be assigned to either:

- **ED-dispensing with home supervision** (control): Participants will receive 2-3 medications:

  1. Oral prednisolone based on body weight to achieve a daily dose of 2mg/kg/day not to exceed 40 mg per day for 5 days or its equivalent (provided in the emergency department),
  2. 360 μg of budesonide inhalation powder once-daily for at-home use, and
  3. albuterol sulfate as needed for relief of acute respiratory symptoms.

  Given 120 doses per budesonide inhaler at 2 puffs per day, two inhalers will be dispensed therefore ensuring $\geq$90 days of medication coverage. Once-daily budesonide at 360 μg per day has been shown to be safe and efficacious by several randomized controlled trials for the treatment of mild-to-moderate asthma. All participants will be advised and/or scheduled to complete a follow-up visit with their child's healthcare provider within 7 days of ED discharge. The ED staff will communicate with healthcare providers to inform them of the child's study participation and their assigned medication regimen. Parents will also receive a copy of the letter to take to their child's follow-up visit. Each participant will receive general asthma education including specific training on how to use the inhaler.

- **ED-dispensing with home and school supervision** (intervention): Participants will receive care as described above for home use and additional inhalers will be couriered to the child's school health office within 5 business days after ED discharge. School health personnel will supervise the child's use of once-daily

budesonide each school day that the child is present. Parents will be instructed to supervise their child's at-home use only on weekends, holidays, and school absences.

Consenting participants may already be taking an inhaled corticosteroid at the time of ED arrival. At ED discharge, their current inhaled corticosteroid will be discontinued and replaced by the study's budesonide inhalation powder.

The school health office will also receive an Asthma Action Plan that details the participant's medication regimen, explains how to recognize and respond to worsening asthma symptoms, and describes when to activate the emergency medical services system. The Clinical Site PI's name will be listed on the Asthma Action Plan and school health personnel will be encouraged to facilitate follow-up with this practitioner if needed. Training will be made available to school nurses, health assistants, and/or administrative personnel that provides general asthma knowledge and demonstrates proper inhaler technique. In our experience, even after viewing the web-based training, school health personnel may have remaining questions about proper inhaler technique or need reinforcement of appropriate asthma management techniques. Therefore, we will establish a toll-free "hotline" staffed during school hours for the clinical centers involved (eastern and central time zones) by experienced school health research personnel at the ED-SAMS outreach unit at the University of Arizona to address unanswered questions. Anticipated advice will include proper inhaler technique and storage, communication strategies for engagement of the child's healthcare provider, and general asthma management. We will take care to ensure school personnel do NOT use the hotline in lieu of 911 for the treatment of asthma emergencies.

To ensure medication reaches the participant's school in a timely manner, the ED personnel will forward the information needed to initiate school-supervised treatment to the ED-SAMS outreach unit at the University of Arizona. The ED personnel will also complete the necessary steps to initiate medication administration including:

1. preparing the medication with a personalized label, administration instructions, and the prescribing physician's name and

2. completing the district's required medication administration records which typically require signatures from parents and sometimes physicians.

With the support of the ED-SAMS Outreach Unit sites will ensure that all necessary forms are available at each ED. Within 5 business days of randomization, while school is in session, the following will happen: the school health office will be contacted to:

1. confirm initiation of medication administration,

2. communicate the method and timing of medication delivery, and to

3. arrange web-training for personnel with administration authority.

Once confirmation is received, medication will be released by hospital courier delivery to the school's health office. To accomplish these activities, we will rely on our experience developing similar protocols in other populations and settings.[6]

5.2 Withdrawal From Study

Parents may withdraw their child from participation in this study at any time. We will not be able to collect new information about their child, and they will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

6 Data Analysis

The hypothesis of this preliminary study is that ED-SAMS will be feasible to conduct, and it will be acceptable to the providers, schools and families.

ED-SAMS is hypothesized to reduce exacerbation risk by increasing adherence with daily controller medication. There are 4 major outcomes of interest: our ability to recruit and retain participants, our ability to initiate school-supervised medication administration, and participant satisfaction. We will also conduct a preliminary CEA to identify potential cost-centers, refine measurement procedures, and inform future decision modeling.

This pilot trial is intended to inform the design of a larger multi-center clinical trial that capitalizes on the full experience, infrastructure, and reach of the 18 PECARN sites. The future trial is anticipated to be a multi-center randomized controlled 3-arm trial where children are randomized to receive ED-based prescribing with home supervision (guideline concordant care and control arm) or ED-based dispensing with home supervision or ED-based dispensing with home and school supervision. This design allows the impact of dispensing to be differentiated from the mode of supervision. Because our current goal is to determine feasibility, we have included the two intervention arms: ED-dispensing with home supervision and ED-dispensing with home and school supervision.

Ninety children (45 per arm) from 3 participating EDs will be randomized to receive ED-dispensing with home supervision or ED-dispensing with home and school supervision. The primary outcome, 90-day ED recidivism, will be obtained from medical record review; 60-day and 30-day recidivism will be evaluated as secondary outcomes. The purpose of estimating the potential impact of the intervention on 90-day recidivism is three-fold: ensure that recidivism can be accurately tracked among this population of children, estimate which follow-up period is most sensitive to the intervention, and estimate a plausible effect size. These elements inform feasibility of ED-recidivism as an outcome and help establish an appropriate sample size for a planned larger clinical trial.

6.1 Specific Aim Analyses

Specific Aim 1. Determine the feasibility and acceptability of dispensing inhaled corticosteroids in the emergency department and supervising its use in the school setting.

There are 4 important areas of interest: recruitment feasibility, intervention feasibility, participant retention, and intervention acceptability. Assessing the extent to which we can accomplish our goals and successfully engage with families, schools, and clinicians will help determine the appropriateness and design of a future multi-center randomized controlled trial.

The PECARN Registry will be used to summarize school-aged asthma patients seen in participating PECARN Registry Emergency Departments (EDs) for active asthma exacerbations in years 2016 and 2019. The total number of asthma visits seen by each ED will be summarized along with insurance status and current medications being taken by patients. Information about controller medications collected in the Registry will be evaluated and categorized in order to define the type of controller medication in use at the time of the ED Visit. Data will be summarized for each ED using summary statistics (means/medians and frequencies/percents). The primary outcome is whether or not a child is on monotherapy at the time of ED arrival. Statistical tests (e.g., chi-square and Cochran-Mantel-Haenszel tests stratified by ED) will compare characteristics of asthma patients between the two years. Individual chi-square tests will be reported for the primary outcome for each hospital. Sensitivity analyses will also be performed looking at the data in aggregate.

Specific Aim 2. Estimate a range of plausible intervention effect sizes to support the development of a larger multi-center clinical trial.

While the primary purpose of the ED-SAMS pilot is to determine the feasibility and acceptability of the proposed intervention, we will also estimate the confidence interval of the intervention's effect size. We are aware that small samples such as this one yield large standard errors and wide confidence intervals. However, we still believe this pilot data will be informative with regard to the intervention's potential impact and whether future trials are likely to hold promise. Furthermore, the results can inform future analytic approaches and suggest a plausible range of potential effect sizes. As such, the focus will not be on significance testing but rather on estimating effect sizes and corresponding confidence intervals. Enrollment rate (subjects enrolled out of those eligible during enrollment windows) will be estimated using the observed proportions and exact binomial 95% confidence intervals. Rates of ED recidivism within 90 days and corresponding confidence intervals will be estimated in a similar fashion.

Specific Aim 3. Conduct a preliminary cost-effectiveness analysis (CEA).

The primary outcome will be dollars per averted ED visit. ED visits are an objective measure of exacerbation risk that are salient to patients, payers, and policymakers. While ED visits themselves represent only 5% of asthma-related health spending, the ED is the primary access point to costly inpatient care. For example, the mean cost of an asthma-related ED visit is approximately $600; however, about 15% of children treated in the ED are admitted for inpatient care which costs about $4000 per inpatient stay. Therefore, averting a single ED visit could yield $1200 in cost-offsets ($600 plus 15% of $4000).

To the extent possible, the analysis will follow the International Society for Pharmacoeconomics and Outcomes Research best practices for CEA conducted alongside clinical trials. However, this analysis will deviate from these recommendations in two important ways. First, the primary outcome is not a comprehensive measure of well-being (e.g., quality-of-life) that captures all of the relevant impacts of asthma. While this recommendation is well-founded, there are no existing instruments that can reliably capture quality-of-life, or more specifically, the preference-based utility weights needed to derive quality-adjusted life-years. We (Joe K. Gerald and Lynn B. Gerald) have considerable experience using the Pediatric Asthma Health Outcome Measure, a tool designed to prospectively capture quality-adjusted life-years in children with asthma. We have found it to be difficult to administer and its measurement properties unsuited for its intended role. Lacking a suitable alternative, we have chosen to rely instead on averted ED visits. In a second major deviation, we have chosen to use the payer, rather than societal perspective. The major implication of this decision is to ignore benefits that might accrue to patients and their families, meaning we will tend to underestimate the

intervention's cost-effectiveness. We recognize this as an important limitation, but we also recognize that society does not "write checks". Our primary intention is to demonstrate to third-party payers that their investment could be worthwhile. The time horizon will comprise the 90-day treatment window as we anticipate all intervention benefits and costs will accrue during this window. Because of the short time horizon, it will not be necessary to discount future costs or benefits.

A decision-analytic model will be developed that incorporates not only the point estimates of the various parameters but also the uncertainty surrounding them (e.g., 95% confidence interval). In addition to standard one-way and two-way deterministic sensitivity analysis, the model will also use a probabilistic sampling strategy to estimate overall model stability and generate a pseudo-95% confidence interval based on multiple iterations (e.g., 10,000 runs). This strategy will help identify the most influential model assumptions and those parameters that if estimated with greater precision would meaningfully improve the model's predictive power.

All resources required to implement school-based supervision will be measured including medication courier fees. Asthma-related medical costs (e.g., ED visits) will be estimated using a gross-costing method where costs are bundled by service type (e.g. $600 per ED visit) rather than micro-costing where costs are individually aggregated (e.g. nursing time, medication, procedure costs at each ED visit). Gross-costing is more practical and reliable than micro-costing when a wide variety of service events and locations are being measured. Our primary source of cost data will come from medical record review to identify asthma-related ED visits; however, this will be supplemented by research logs (e.g. intervention-related personnel time and courier fees) and parent interviews (e.g., prescription fills for ICS albuterol among the control group). Where possible or needed these data will be crosschecked against existing estimates from secondary sources such as the published literature.

6.2 Sample Size Calculations and Statistical Power

Randomization of 90 patients allows estimation of consent and approach rates to within 8% (half-width of 95% confidence interval). With 45 subjects in each arm, we will be able to estimate recidivism to within approximately ±15%.

6.3 Populations for Analysis

The subjects for the proposed research are children 6-12 years of age who are treated for an asthma attack as determined clinically by the principal ED provider (e.g., shortness-of-breath, cough, wheezing that improves following ≥ 1 dose of albuterol or equivalent and ≥ 1 dose of systemic corticosteroids). The child's symptoms must resolve so that he/she can be safely discharged home. Children must have physician-diagnosed persistent asthma as reported by the child's parents and/or recorded in the clinical site's electronic medical record. Children must be enrolled full-time (5 days/week) in a participating school and must be 6-12 years of age with a physician diagnosis of asthma. Parents and children must speak English or Spanish. We expect the children to be 40% female, 30% Hispanic, 54% black and 45% white (30% are Hispanic White).

We expect children to be 40% female as is the national population of asthma among children; therefore, females will be adequately represented. We expect that approximately 84% of the children who enroll will be minorities: including approximately 54% black and 30% Hispanic. Therefore, minorities will be well represented in this research.

7 Data Management

7.1 Clinical Site Selection

In this pilot study, children treated within 3 of 18 participating PECARN EDs will be targeted for recruitment. These sites were selected based on their ability to demonstrate feasibility within a diverse geographic locale, setting, and/or population. Each of these sites will be collaborating with the largest public school system in their catchment area.

7.2 Electronic Data Capture System

Under the direction of the DCC PI and biostatistician, and in collaboration with study investigators, the DCC will be involved with the development of electronic data capture systems to collect information on screening and enrollment, survey responses, safety measures, and medical chart review. The DCC uses a web-based interface designed specifically for clinical trials and observational studies. The DCC has developed a sophisticated software system for managing data discrepancy queries. This Query Management System allows for data checks on individual data fields (e.g., for missing or out-of-range data) in addition to the validation of data between different forms. This helps ensure that data will be complete and valid.

7.3 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. The DCC will plan to perform remote monitoring activities during the study period to ensure regulatory compliance, patient safety, and the quality of the data collected. Remote monitoring will involve a detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator. Regulatory documents, data collection forms and parts of the medical record may be reviewed to compare those materials against the data recorded in the electronic data capture system.

Remote monitoring will take place depending on grant budget, site enrollment and compliance issues identified. Each site will be provided with a written report, and sites will be required to follow up on any deficiencies.

Remote monitoring documents will be retained in accordance with federal requirements. Safety of subjects will be monitored and ensured in accordance with the Data and Safety Monitoring Board (DSMB) plan.

7.3.1 Pharmacy Monitoring

The Clinical Center pharmacy must maintain adequate records of all dispensed study drug. Each pharmacy will be monitored and may be requested to send copies of these documents to the DCC.

7.4 Data Coordinating Center

7.4.1 Data Center Description

The DCC in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the-art, energy-efficient data center completed in 2013. The data center facility supports more than 1400 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The new data center was built using high industry standards and energy-efficient cooling solutions. The data center is cooled by Rittal's LCP inline cooling technology, providing efficiency, redundancy and modularity. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains a redundant Mitsubishi uninterruptible power system with a diesel backup generator. The data center is protected with a FM200

fire suppression system, early warning smoke detectors and a heat detection warning system to act as a secondary system to the smoke detectors. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

In 2011 the data center began a large scale VMware server virtualization deployment. Currently, the data center has virtualized about 99% of its environment. The virtual environment consists of more than 200 virtual servers. The data center's virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.
- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware or software.

The data center also enhanced its storage resources by implementing a networked storage system to support its virtualized environment. The data center currently manages over 50 terabytes of data. The storage solution consists of Dell's EqualLogic PS Series Storage system for providing a virtualized storage area network. Some of the benefits that are realized through this technology are:

- storage architecture is no longer a bottleneck for IT services;
- performance is better than with the previous architecture;
- tiered storage is now possible;
- provisioning and reclamation of storage area network disk will be much easier; and most important,
- the new architecture includes a redesign of the storage area network fabric to include complete redundancy.

Production servers running critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. DCC storage area networking applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday.

Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

In the event of catastrophic failure, such as a fire in the server facility, daily backups would probably survive because of the fire suppression system and fireproof safe, but there would be obvious delay in re-establishing data center function because the servers will not survive such a disaster. Total destruction of the data center facility could cause the loss of up to one week's data. In future investments, the data center is making co-location, disaster recovery and business continuity solutions a top priority.

DCC information systems are available 24 hours a day, 7 days a week to all users unless a scheduled maintenance interruption is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

7.4.2 Security and Confidentiality

The data center coordinates the network infrastructure and security with the Health Sciences Campus information systems at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2012 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using transport layer security or virtual private network technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the transport layer security protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a virtual private network client.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with Windows 2012 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems, before access is provided.

The limited PHI in the PECARN registry analysis database (month, year) is used in order to direct performance measure reports, and the month and year of visit will not be included in the database produced for sharing with other researchers.

Database access database is managed in accordance with PECARN data sharing policies and applicable Federal laws. The registry data will be de-identified and it will not be permissible for any investigator to attempt to re-identify data within the registry.

7.5 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the DCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives (when applicable) of the Food and Drug Administration (FDA), NIH, other Federal funders or study sponsors, and the Institutional Review Board (IRB) for each study site.

8 Protection of Human Subjects

8.1 Institutional Review Board Approval

The University of Utah IRB is the IRB of record for ED-SAMS. Each clinical center will seek approval from their local IRB to defer oversight to the University of Utah IRB. The DCC will track IRB approval status at all participating centers and will not permit

subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

8.2 Informed Consent

We will recruit children from the 3 participating EDs. Research staff will approach parents of children between the ages of 6 and 12 who are being treated for acute respiratory distress consistent with an asthma attack. The research staff will explain the study and will provide parents with a brief written description. Written consent will be obtained from parents; assent will be obtained from children as applicable. Copies of the consent and assent will be provided to the parents. Recruitment and study procedures will occur during down times to avoid interfering with clinical care. Given a 6-hour turn-around window (time from ED presentation to discharge) within PECARN EDs, we anticipate adequate time will be available to identify, recruit, and evaluate study participants. To ensure all participants can complete 90 days of school-supervised treatment before summer break, recruitment will commence at the beginning of the school year (e.g., September) and cease in March. Schools will be approached at the district level for initial support. Parents will provide consent for us to contact the school on their behalf and will complete the necessary paperwork for the school to initiate supervised therapy.

Parental Permission

Subjects who are eligible for this study are at most 12 years of age, and written permission from parents or legal guardians will be required for participation. After determining that a subject is eligible, the site investigator or designee will approach the parent or legal guardian to offer participation for their child to be in the study. The parent or legal guardian will be informed about the objectives of the study and the potential risks and benefits of participation. If the parent or legal guardian refuses permission for their child to participate, then all clinical management will be provided by the clinical staff in accordance with institutional practice and judgment.

Child Assent

Assent will be obtained, as applicable from children who are eligible for this study.

8.3 Potential Risks

The major risk to the study is loss of confidentiality. However, we will minimize these risks through appropriate protection of all study data (see protection against risk).

There are risks related to prescribed asthma medications, however, these risks are associated with standard of care. The majority of children receiving daily medication at school will likely have previously used inhaled corticosteroids. The primary risk from inhaled corticosteroids is a yeast infection in the mouth, commonly known as thrush. Children and parents will be taught that the child should rinse his/her mouth after taking their inhaled steroid to reduce this risk and school health personnel will also be instructed about this risk during the web-based training.

Other adverse events with a $\geq 1\%$ occurrence reported by patients include colds, sore throat, nasal congestion, sinusitis (sinus infection), headache, nausea, upset stomach, voice changes, back pain, fever, indigestion, and ear infections. Rare instances of glaucoma, increased pressure inside the eye, and cataracts have also been reported with long-term use. Studies have also shown that inhaled corticosteroids may cause a reduction in the rate of growth in children. The potential for growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks and benefits associated with alternative therapies. Growth should be monitored in children who receive corticosteroids.

Rare side effects of ICS include: immediate and delayed hypersensitivity reactions including a red, itchy rash, hives, swelling of the face and lips, and difficulty breathing, symptoms of hypocorticism (extreme fatigue, weight loss, abdominal pain), and hypercorticism (weight gain, easy bruising of the skin); psychiatrics symptoms including depression, aggressive reactions, irritability, anxiety, and psychosis.

Children will also be taking quick relief medication (albuterol) as needed. Albuterol is very commonly prescribed for children with asthma (almost always). Albuterol may cause jitteriness, dizziness and can raise the heart rate after administration. Parents and school health personnel will be educated on the risks of all asthma medications to reduce risks to the children.

8.3.1 Known Potential Benefits

The benefits for the children may include an increased knowledge about their asthma and how to control it as well as reduced asthma exacerbations.

8.3.2 Assessment of Potential Risks and Benefits

All study information will be confidential. Privacy risks will be minimized by appropriate protection of all study data. Paper data will be stored in a locked file cabinet and

computerized data will be stored on a secure server with password protection. Access to study data will only be given to study personnel. Data will only be published in aggregate form such that no individuals can be identified. Because the study is a multi-site clinical trial, the National Heart, Lung and Blood Institute (NHLBI) requires a DSMB. This Board will set the rules and protocols for medical intervention.

The benefits for society include increased knowledge about methods that may reduce asthma exacerbations. The project will also provide information regarding the cost of this program.

8.4 Adverse Events, Serious Adverse Events and Unanticipated Problems

8.4.1 Adverse Events

This study is using guideline concordant care for asthma. The study intervention is not related to the drugs used in the study, rather the efficacy of school-based supervision. The PIs, DCC, and Clinical Coordinating Center will monitor the study for any trends, but adverse events would likely be attributed to the underlying disease of asthma, not the school-based supervision.

Definition: An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. The site investigators will evaluate all adverse events. The study staff will obtain information on symptoms and adverse events on scheduled follow up calls and text message surveys. Adverse events not previously documented in the study will be recorded on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established.

Side Effects: Study staff will obtain information about side effects on scheduled follow up calls and text message surveys.

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the following criteria. *Relatedness may not be assessed by a research coordinator, and must be assessed by an investigator.*

Not Related: The event is clearly related to other factors, such as the subject's

clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Seriousness: The severity of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An adverse event is considered expected if it is known to be associated with acute asthma, other underlying medical conditions of the subject, is directly related to study outcome, or is otherwise mentioned in the protocol, informed consent, investigator brochure, or other study documents. Expected complications of asthma treatment include yeast infection in the mouth, commonly known as thrush, jitteriness and dizziness after administration of ICS, elevated heart rate, respiratory infection, pharyngitis, sinusitis, voice alteration, headache, flu syndrome, pain, back pain, fever, dyspepsia, gastroenteritis, and nausea.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of corticosteroids. Rare side effects of ICS include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis,

urticaria, angioedema and bronchospasm, symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety, and psychosis.

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Intervention: Surgery or procedure
- Other Treatment: Medication initiation, change, or discontinuation
- None: No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

The following adverse and serious adverse events are expected:

Adverse Events

- Evidence of coercion to participants
- Oral Thrush (white tongue)
- Worsening of respiratory symptoms (i.e., coughing, wheezing, shortness of breath, tightness in the chest during the day, waking up from sleep at night) requiring healthcare evaluation

Serious Adverse Events

- Hospitalization due to asthma
- Death for any reason

8.4.2 Time Period for Adverse Events

Serious adverse events, unexpected medically attended events, and new onset chronic illnesses will be recorded following randomization through 120 days. Specifically, events that occur following parental permission to participate in the study, but prior to actual randomization, are not adverse events.

8.4.3 Data Collection Procedures for Adverse Events

After patient randomization, all adverse events (including serious adverse events), whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition present at the time of randomization, recorded at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the DCC because this requires specific training.

8.4.4 Unanticipated Problems

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The site investigator will report unanticipated problems to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the NHLBI Program Official or Project Officer in an expedited manner (within 24 hours). In accordance with local IRB requirements, the site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the DCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NHLBI staff cannot be reached expeditiously, the DCC will notify the study investigators and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB.

8.4.5 Monitoring Serious Adverse Events

The Principal Investigator of the DCC (Dr. Dean) will act as the medical monitor for this study. If Dr. Dean is unavailable, a qualified physician will be designated to fulfill this function. Site investigators and/or research coordinators will report serious adverse events to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign each SAE report after review. All SAE reports will be retained at the DCC, and all SAE reports will be available for review by DSMB members and NHLBI staff. In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, NHLBI staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or if the NHLBI staff and the DSMB chairperson cannot be reached expeditiously, the DCC will notify the study investigators and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the DCC. After notification of the NHLBI Program Official or Project Officer, and the DSMB chairperson, of serious, unexpected, and study-related AEs or UPs, decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigators and all clinical investigators, who will be instructed to report this to their local IRB.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The DCC will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

8.4.6 Follow-up of Serious, Unexpected and Related Adverse Events

All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study or discharge from the hospital, will be followed by the Clinical Center investigators until the events are resolved, subject is lost to follow-up, the adverse event is otherwise explained or has stabilized.

9 Data and Safety Monitoring Plan

9.1 Data Safety Monitoring Board

The purpose of the DSMB is to advise the Federal funding agency NHLBI, the ED-SAMS PIs (Dr. Gerald and Dr. Denninghoff), and the PECARN Executive Committee regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB will be responsible for monitoring accrual of study subjects, adherence to the ED-SAMS protocol, assessments of data quality, performance of individual clinical sites, and review of serious adverse events and other subject safety issues.

DSMB meetings to evaluate study protocols, prior to study implementation, may be open or closed according to the decision of the DSMB members. We suggest that these meetings should be open to members of the ED-SAMS investigative team, as there are no confidential components to these proceedings, and it will facilitate the review and appropriate alterations of the protocol in response to DSMB concerns.

9.2 Planned Interim Analysis

At the current time no interim analysis is planned. This is a pilot study involving recruitment over a short period of time. There would be insufficient time or data to analyze, present, then act upon. If the DSMB and their charter require an interim analysis, we will do so.

9.3 Study Discontinuation and Closure

Based on prospectively defined guidelines to be outlined in the DSMB charter, as well as any additional information available to DSMB members, the DSMB should recommend whether to terminate enrollment in ED-SAMS because of potential safety concerns.

In the unlikely event that the DSMB recommends emergent cessation of enrollment in ED-SAMS because of safety concerns, this communication will be made during the debriefing segment of the DSMB meeting. If the NHLBI staff concur with this recommendation, the DCC will notify all ED-SAMS clinical sites to cease enrollment immediately.

10 Study Training

10.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The DCC, in collaboration with the study investigator (Dr. Gerald), will be the main contact for study questions.

11 Regulatory Issues

11.1 Food and Drug Administration

Pulmicort ICS (budesonide) is indicated for twice-daily use; however, for this study we are testing the hypothesis that once-daily supervision of ICS (budesonide) will improve asthma related outcomes. We are requesting an IND exemption for the following reasons:

- This study is NOT intended to be reported to the FDA in support of a new indication.
- This drug is lawfully marketed as a prescription drug product.
- This study is NOT intended to support a significant change in advertising for the product.
- The study does NOT involve a route of administration or dosage or population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug. This study will change the administration of drug from twice a day to once a day, however, the daily dose will remain as approved. This will not significantly increase the risk.

11.2 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth, date of medical care and contact information (including names). Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de-identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the de-identified research data sets that will be used for analyses, all study sites will be offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

11.3 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

11.4 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

11.5 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research, or in accordance with State law. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

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