Statistical Analysis Plan

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

Protocol Version and Date: 1.02; March 15, 2019

SAP Author: John M. VanBuren, Ph.D.

SAP Version and Date: 1.01; August 12, 2019

SAP Version 1 Date: November 26, 2018

CONFIDENTIAL

Approvals:

Approved By:

Name	Title	Date
Name	Title	Date

SAP Revisions:

Version 1.00 to 1.01

- Sections 3.1, 3.2, 3.3, 4.2.3, and 7.3.2 have been updated to reflect the change in arms from ED-prescription to ED-dispensing.
- Section 3.3 has been updated to include the 120 day phone call that will occur.
- Section 6.1 removed the sentence regarding an interim DSMB meeting during the Summer of 2019 since enrollment did not start during the previous school year.
- Section 7.2.1 has been updated to remove the concept of two interrupted screening periods since enrollment will occur during one school year.
- Section 7.2.5 has been updated to collect ED physicians satisfaction on every patient instead of just the home and school arm since there is no standard of care group anymore.

Contents

Abbreviations

Abbreviation	Definition
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
ED-SAMS	ED-Initiated School-Based Asthma Medication Supervision
ICS	Inhaled CorticoSteroid
ITT	Intent-To-Treat
PP	Per-Protocol
(S)AE	(Serious) Adverse Event
SAFETY	Safety Population
SAP	Statistical Analysis Plan
SCREEN	Screening Population

1 PREFACE

1.1 Purpose of SAP

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the protocol: ED-Initiated School-Based Asthma Medication Supervision(ED-SAMS).

The structure and content of this SAP provides sufficient detail to meet the requirements and standards set by the Data Coordinating Center (DCC).

1.2 Auxiliary/Other Documents

The following documents were reviewed in preparation of this SAP:

- Protocol: ED-Initiated School-Based Asthma Medication Supervision.
- Case Report Forms (CRFs) for the ED-SAMS protocol

The reader of this SAP is encouraged to read the protocol for details on the conduct of this study, and the operational aspects of clinical assessments.

The purpose of this SAP is to outline the planned analyses to be completed for the ED-SAMS trial. The planned analyses identified in this SAP will be included in future study abstracts and manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed. Any post hoc, or unplanned, analyses not explicitly identified in this SAP will be clearly identified as such in any published reports from this study.

It is possible that, due to updates or identification of errors in specific statistical software discussed in this SAP, the exact technical specifications for carrying out a given analysis may be modified. This is considered acceptable as long as the original, prespecified statistical analytic approach is completely followed in the revised technical specifications.

2 STUDY OBJECTIVES AND OUTCOMES

2.1 Study Objectives

2.1.1 Primary Objective(s)

The primary objectives of the ED-SAMS trial are to:

1. Determine the feasibility and acceptability of dispensing Inhaled CorticoSteroids (ICS) in the Emergency Department (ED) and supervising its use in the school setting.
2. Estimate a range of plausible intervention effect sizes to support the development of a larger multi-center clinical trial.
3. Conduct a preliminary cost-effectiveness analysis

2.2 Study Outcomes

2.2.1 Primary Outcome(s)

The primary outcomes of this study are:

- The number of subjects recruited within two interrupted 3-month periods;
- The number of business days needed to initiate supervised ICS use in the school setting;
- The number of subjects retained for the 90-day intervention period;
- Asthma symptom data during the study period; and
- Caregiver, school, and ED provider satisfaction within the ED-SAMS program.

2.2.2 Secondary Outcome(s)

Secondary outcomes of this study are:

- Ninety-day ED-recidivism and
- A preliminary cost-effective analysis of treatment.

2.2.3 Safety Outcome(s)

There are no formal safety analyses for ED-SAMS.

3 STUDY DESIGN AND METHODS

3.1 Overall Study Design

The ED-SAMS study is designed to evaluate the feasibility and acceptability of ED-initiated school-based asthma medication supervision 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-based ICS dispensing with home supervision or ED-initiated ICS dispensing with at-home and at-school supervision. All children will be treated with a

standard medication regimen consisting of once-daily budesonide inhalation powder supplemented by as-needed albuterol sulfate.

To ensure a random selection of participants, each ED will screen patients during prespecified windows scheduled by the DCC. In order to avoid enrollment bias, a randomized screening schedule for each site will be created based on the availability of research staff and local census patterns.

3.2 Method of Treatment Assignment and Randomization

Eligible and consented participants will be randomly assigned on a 1:1 basis to receive either ED-dispensing with home supervision or ED-dispensing with home and school supervision. The randomization protocol will be created by the DCC biostatistician using a block permutation of lengths 2, 4, and 6 stratified by site to ensure balanced randomization given the small sample sizes required at each site.

3.2.1 Delivery of Randomization and Emergency Backup

Randomizations will be delivered to the clinical centers using the website randomize.net. This system will use each enrolled patient's clinical center to deliver the next assigned treatment.

In this trial, there will be no "emergency backup" randomization, as we expect to be able to capture a sufficient number of patients.

3.2.2 Handling of Incorrect Randomization in Study Analyses and Reports

Participants will be analyzed and reported in an Intention to Treat (ITT) framework as described in Section 4.2.2.

3.3 Treatment Masking (Blinding)

The ED-SAMS study is necessarily performed in an unblinded fashion. Study personnel at the ED-SAMS sites involved in the patient's treatment and follow-up (including child's school) will be unblinded to the assigned treatment strategy. The school staff will not be notified of a subject's involvement in the study if the subject is randomized to the ED-based ICS dispensing with home supervision arm, but it is possible that they find out about the enrollment if the subject or the subject's family voluntarily divulges this information or find out through other means.

The personnel at the University of Arizona ED-SAMS Outreach Center will be aware of the subjects enrolled and the randomization group assigned. In particular, they will receive the following information on all subjects:

- Subject's full name
- Subject's date of birth
- Subject's school name
- Subject's school address
- Subject's family contact information

The ED-SAMS Outreach Center will perform follow-up interviews by telephone approximately 30, 60, 90, and 120 days after enrollment. The Outreach Center will ask parents about their child's medication compliance and asthma related events (e.g., hospitalization).

The DCC study team will be unblinded to individual treatment assignments (through randomization notification emails), but knowledge of arm-specific aggregate treatment results will be limited to biostatisticians involved in the analyses (i.e., non-biostatistician DCC members will not be unblinded or aware of results).

4 STUDY SUBJECTS AND ANALYSIS POPULATIONS

4.1 Eligibility

Inclusion criteria for the ED-SAMS study 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. The child's symptoms must improve following $\geq$1 dose of albuterol and $\geq$1 dose of systemic corticosteroid such that he/she can be safely discharged home; AND
4. The child must have physician-diagnosed asthma as reported by parents or documented in the electronic medical record.

Exclusion criteria are:

1. Child is not in a participating school; OR
2. Child is not a full-time student (5x/week); OR

3. Child is enrolled in another research study; OR
4. Child is hospitalized; OR
5. Child or consenting parent/guardian does not speak English or Spanish; OR
6. Child's asthma is too severe to safely participate as evidenced by prior ICU admissions in the past year; OR
7. Child has a history of $\geq$2 hospitalizations for asthma in the past year; OR
8. Child has a history of $\geq$2 controller medications for asthma; OR
9. Parent does not have a cell phone; OR
10. Parent cannot send and receive text messages.

4.2 Populations for Analyses

4.2.1 Screening Population

The screening population (SCREEN) includes all patients who are screened for eligibility into the trial, regardless of randomization into the trial or treatment status. This population represents all patients who meet inclusion criteria outlined in the study protocol and who are screened in real-time by study staff at the site. This population will be used for reporting of study flow per CONSORT guidelines.

4.2.2 Intention-to-Treat Population

The ITT population includes all subjects who are randomized into the trial, regardless of adherence to the protocol, including, for example, subjects who do not use their inhaler or subjects who do not receive the inhaler at school. The ITT population will be used for the primary efficacy analyses in the study, as well as for main efficacy analyses of secondary and tertiary outcomes. All analyses using the ITT population will be based on each subject's assigned treatment arm, regardless of treatment actually received.

4.2.3 Per-Protocol Population

The per protocol (PP) population includes all subjects randomized to the ED-dispensing with home supervision arm as well as the subjects randomized to the ED-dispensing with home and school supervision arm who received medication at school at least 80% of the days for which they were expected to receive. For example, assume a subject is randomized to the ED-dispensing with home and school supervision arm and based on their enrollment date and 90-day supervision end date, they were supposed to receive 50 days of school supervised therapy (after accounting for school holidays, national holidays, and weekends). If they were

at school and received therapy for at least 40 days during the 90 days of follow-up, then they would be included in the PP analysis ($50 * 0.8 = 40$ days required).

4.2.4 Safety Population

The safety (SAFETY) population includes all subjects who are randomized. Reporting of results based on this population will be summarized according to treatment received (e.g., whether or not the treatment was sent to the school and home). This population will be used for analysis of adverse events and (in addition to ITT) to examine safety outcomes.

5 GENERAL ISSUES FOR STATISTICAL ANALYSES

5.1 Analysis Software

Analysis will be performed using SAS® Software version 9.4 or later whenever possible. Other software packages, including R, may be used for particular specialized procedures.

5.2 Methods for Withdrawals, Missing Data, and Outliers

Per the ITT principle, subjects who withdraw from the study will have all available data used in the analysis. In the event that a substantial number of subjects are withdrawn, baseline characteristics and available information on hospital course will be reviewed and compared to subjects not withdrawn, to assess empirically if these subjects differ from those remaining in the study for the scheduled treatment and follow-up time. Even if the subject stops contributing data due to loss to follow-up, their data will still be used in analyses.

Outliers will be reviewed for validity. Outliers that are valid, for example, high laboratory values, will be included in all primary reports from this trial.

Missing data will remain missing instead of being imputed. This will help the investigators understand the rates of missingness when planning the larger trial.

5.3 Multiple Comparisons and Multiplicity

Because the goal of the pilot study is to assess safety, feasibility, and preliminary efficacy results, adjustment for multiple comparisons will not occur. All other analyses will be considered exploratory in nature and multiple comparisons will not be done.

Safety outcomes for this study will be reported using unadjusted p-values for each individual comparison. However, all reports of these outcomes, to the DSMB and in published reports, will explicitly note that multiple safety outcomes have been evaluated. Formal multiplicity-adjusted significance assessments for these safety outcomes will be performed upon request of the DSMB or other reviewers.

5.4 Planned Subgroups, Interactions, and Covariates

There are five subgroup factors prespecified for analysis in this trial. These analyses are exploratory and no definitive conclusions should be made from the results. These subgroups are:

- Ethnicity
- Race
- Age
- Gender
- BMI

5.5 Independent Review

All statistical analyses for primary reporting of trial results will be independently verified through dual programming. Two statisticians will each program all datasets and analyses for the DSMB reports and the primary manuscript(s) and the results will be compared. This process will begin at the analysis design stage and will continue through writing of abstracts and manuscripts.

6 INTERIM ANALYSES

6.1 Frequency of and Timepoints for Interim Analysis

This study has two planned DSMB meetings. The first meeting will be prior to study enrollment and the second meeting will occur upon the completion of study enrollment. The DSMB has the discretion to alter timing and frequency of meetings. The DSMB will have a charter and approve the protocol prior to implementation.

6.2 Stopping Rules for Interim Efficacy Analysis

No rules for stopping for efficacy will be implemented since this is a pilot study.

6.3 Futility Monitoring in the Interim Analysis

No rules for stopping for futility will be implemented since this is a pilot study.

6.4 Subgroups in the Interim Analysis

No formal subgroups analyses in a DSMB report will occur unless requested by the DSMB.

6.5 Blinding in the Interim Analysis

Data center biostatisticians involved in this study will be unblinded and aware of results by treatment. Other DCC personnel will receive individual treatment assignments (through randomization email notifications) but will be blinded to aggregate results. The DCC study team for this trial will have access to individual safety and efficacy data. Personnel at the clinical centers will be blinded to aggregate safety and efficacy data until the time of final analysis or until the decision is made to unblind all investigators to the study results.

7 PLANNED ANALYSES

7.1 Description of Subject Characteristics

Publication of the primary results will include reporting of key baseline characteristics overall, and by assigned treatment arm. These will include, but are not limited to:

- Ethnicity;
- Race;
- Age;
- Gender; and
- BMI.

7.2 Primary Outcomes Analyses

The primary outcome for the larger ED-SAMS study is 90-day ED recidivism. For this pilot study, the primary outcomes correspond with feasibility. Each of the five primary outcomes are described in detail below.

7.2.1 Number of Subjects Recruited

Enrollment rates and time to reach the targeted 90 participants will be analyzed. The primary outcome is the number of subjects recruited during the school season. This outcome will be considered successful if 90 participants are enrolled during the windows of screening. Enrollment rates will be calculated based on the dates screening was open. For example, if screening does not occur April through August, then these months do not count towards the 6 total calendar months time (i.e., two 3 month periods). In addition to this binary outcome (able to enroll 90 participants or not able to enroll 90 participants within 6 calendar months), the time it takes to complete enrollment will be recorded.

The number of potential enrollments for a larger study (under various number of sites and enrollment rates) will be calculated using the observed enrollment rate. First, the average number of enrolled subjects per site per enrolling month will be calculated. This is calculated by:

$$\frac{Numberenrolled(e.g., 90) \text{ subjects}}{\text{Total months of enrollment across three sites}} = \text{Average enrollment per site per month}$$

The total time (measured in units of month) spent enrolling will be calculated by summing the date differences between start of enrollment and end of enrollment at each site for each enrollment period (spring/fall).

We anticipate enrollment will occur over 4 years for the larger study. Using the rounded version of the average enrollment per site per month, the following table (Table 1) will be created (displaying other plausible enrollment numbers as well) to display the potential total sample size assuming 4 years of enrollment (enrollment occurring for 6 months per year - September through February). This would result in 24 calendar months per site of enrollment over the 4 year period. The numbers calculated in the table are 24 times the number of sites times the average enrollment per site per month. The actual expected enrollment values used in the column header will be dependent on the results of this study.

7.2.2 Number of Business Days Needed to Initiate Supervised ICS Use in the School Setting

In order for the school to receive the medication after the ED visit, several parties must be notified. Theoretically, within one business day of the ED departure, the ED research team will notify the ED-SAMS outreach unit about the enrollment (so the ED-SAMS outreach unit can ensure all necessary forms are completed). Within three business days of notification, the ED-SAMS outreach unit will contact the school health office to confirm initiation of medication administration and provide guidance on medication delivery. After the discussion with the school health office, the ED-SAMS outreach center will notify the site so

Scenario	Number of Sites	Average Enrollment per Site per Month		
		4	6	8
1	6	576	864	1152
2	8	768	1152	1536
3	10	960	1440	1920
4	12	1152	1728	2304
5	14	1344	2016	2688
6	16	1536	2304	3072
7	18	1728	2592	3456

Table 1: Potential sample sizes in the larger trial

the site can release medication to the school within one business day through courier delivery.

The following times will be summarized:

- Time FROM randomization TO ED-SAMS outreach unit contacting the school regarding student enrollment (excluding holidays and weekends)
- Time FROM ED-SAMS outreach unit contacting the school regarding student enrollment TO ED-SAMS outreach unit notifying the sites to send medication (excluding holidays and weekends)
- Time FROM ED-SAMS outreach unit notifying the sites to send medication TO school receiving medication (excluding holidays and weekends)

The outcome is the sum of the previous three times which will indicate the total number of business days from ED-departure to school initiation. The medication delivery is considered to be successful if at least 90% of the medications are delivered to the schools within 5 business days (when school is in session) of ED discharge (among the subjects randomized to the ED-dispensing with home and school supervision arm).

We will calculate business days as follows:

1. We will create a dataset with every school day in 2019. In this dataset, there will be an indicator of whether it is a business day (i.e., school day). This will incorporate individual school holidays. The weekends and school holidays will be marked as zeros.
2. A separate dataset will contain the raw dates of interest (e.g., ED-departure date, school contact, release of medications)

3. Numbers 1 and 2 will be merged together to identify times specific to each child. The individual child's records will be used to sum the number of business days between each date for the three time periods previously mentioned.

7.2.3 Number of Subjects Retained for the 90-Day Intervention Period

There are three planned follow-up phone calls in this study. The primary outcome for the larger trial is 90-day ED recidivism. Therefore, the 90-day phone call is the most important of the three contact times. For the 90-day call, we will categorize each individual as completing the follow-up call if ALL of the following questions are answered:

Control group:

- Did you fill your child's prescription for rescue medication (albuterol)?
- Did you fill your child's prescription for controller medication (budesonide)?'
- Is your child taking his/her controller medication (budesonide) every day?
- Since we last spoke, has your child been seen by a healthcare provider for follow-up care of their asthma?
- Since we last spoke, did your child experience any of these asthma related events? (note all five options should have a response)

Intervention group:

- When your child is NOT at school, is he/she taking controller medication (budesonide) everyday at HOME?
- Since we last spoke, has your child been seen by a healthcare provider for follow-up care of their asthma?
- Did you discuss your child's participation in supervised therapy at school with your child's doctor?
- Did your child's doctor stop supervised medication at school?
- Since we last spoke, did your child experience any of these asthma related events? (note all five options should have a response)

If any question is not answered within the arm for the 90-day follow-up survey, then the individual will be categorized that they did not complete the follow-up call. The proportion of subjects for whom the 90-day follow-up is considered completed will be summarized overall and by arm.

7.2.4 Asthma symptom data during the study period

Text messaging will be sent on days 30-36, 60-66, and 90-96 after randomization. These texts should correspond with the first attempt at the follow-up phone call. The text message will ask about the child's asthma in the past 24 hours. This text message will be repeated each day for the 7 days. The proportion of texts responded to will be summarized by arm for each of the three periods and then the overall proportions of texts responded to will be summarized.

The number of symptom-free days (number of days where the 'neither' option is chosen) will be summarized per arm per follow-up period. Within an individual, the proportion of symptom free days is calculated for each period and then the average of the child-specific proportions will be summarized.

7.2.5 Caregiver, school, and ED provider satisfaction within the ED-SAMS program

Three different satisfaction surveys will be sent to three supporting populations in the ED-SAMS study. These three populations are:

- Caregivers (e.g., parents)
- School Health Personnel
- ED Physicians

All questions in all the surveys have the following Likert scale response options (with numeric values displayed next to the response):

- Strongly agree (5)
- Agree (4)
- Neutral (3)
- Disagree (2)
- Strongly disagree (1)

Each survey summaries are described in detail below.

Caregivers (parents)
A representative caregiver of each child who is randomized to the ED-dispensing arm with home and school supervision will be asked to rate their satisfaction with the ED-SAMS program at the end of the 90-day period. The following seven questions will be asked:

1. I would recommend ED-SAMS to other parents of children with asthma.

2. My child experienced negative side effects from participating in ED-SAMS.
3. ED-SAMS was a good way to reduce my child's asthma symptoms.
4. I am satisfied with the asthma education I was provided in the emergency department.
5. I am satisfied with the communication that I had with the emergency department as a part of ED-SAMS.
6. I am satisfied with the communication that I had with my child's school as a part of ED-SAMS.
7. I would participate in ED-SAMS again.

The agree responses (i.e., 'Strongly Agree' and 'Agree') indicate support for the ED-SAMS program for all questions except question 2 above which is reverse scored. The Likert scale values will be summarized with counts and frequencies in a table by question and arm. An overall score will be created by averaging the Likert responses (with coded values 1 to 5). Only non-missing items will be used in the averaging. This overall score will use the reverse scoring for question 2 above. The mean and standard deviation of the overall parent satisfaction score will be summarized.

School Heath Personnel

Each school health personnel (there can be multiple personnel from a single school) who assisted in the treatment of a student randomized to the ED-dispensing with home and school supervision arm will be provided a survey at the end of the study. There are eight questions that are asked regarding the satisfaction of the program. These are:

1. I would recommend ED-SAMS to other parents of children with asthma.
2. I would recommend ED-SAMS to other schools.
3. Some children experienced negative side effects from participating in ED-SAMS.
4. ED-SAMS was a good way to reduce children's asthma symptoms.
5. I am satisfied with the information provided to me about how to administer ED-SAMS medications.
6. I am satisfied with the communication that I had with the emergency department as a part of ED-SAMS.
7. I am satisfied with the communication that I had with the child's family as a part of ED-SAMS.
8. I would participate in ED-SAMS again.

The agree responses indicate support for the ED-SAMS program for all questions except question 3 above which is reverse scored. The Likert scale values will be summarized with counts and frequencies in a table by question. An overall score will be created by averaging the Likert responses (with coded values 1 to 5). Only non-missing items will be used in the averaging. The mean and standard deviation of the overall school health personnel satisfaction score will be summarized through a mean and standard deviation.

The results will be broken down by medical license status (have some medical license [DNP, NP, RN, LPN] vs no current medical license) as long as there are at least 5 responses per medical license status group. If there are fewer than 5 responses per group, then only aggregate Likert responses will be presented. Missing license status data will be summarized with the 'no current medical license' group.

ED Physicians

Each ED physician who assisted in the treatment of a subject randomized will be provided a survey after each subject is enrolled. The one question that is asked regarding the ED physician satisfaction of the program is "I would recommend ED-SAMS to other ED physicians."

It is possible that an ED-physician enrolls more than one subject to the ED-SAMS study. If this were to happen, multiple surveys would be collected from the provider, and two different analyses will occur. The first analysis will treat each response as independent and all responses will be used. The second analysis will use only the last response in the summaries. The last response will likely be most representative of their cumulative feelings about the ED-SAMS program.

The agree responses indicate support for the ED-SAMS program. The Likert scale values will be summarized with counts and frequencies. The mean and standard deviation of the Likert responses (with coded values 1 to 5) will also be summarized.

7.3 Secondary Outcome(s) Analyses

7.3.1 Ninety-Day ED-Recidivism

After the follow-up period is completed for each subject, a research team member at the site will review the EHR for the child at the enrollment hospital. The research member will look for indications of return visits to the ED within 90 days of randomization, hospitalizations within 90 days of randomization, and outpatient visits within 90 days of randomization.

Each subject will be categorized by his or her ED-recidivism status based on the EHR review.

The rates of ED-recidivism will be estimated for each arm. The rate along with the exact binomial 95% confidence interval will be summarized. The difference in proportions will also be calculated between arms and an exact 95% confidence interval of the difference will be summarized. No formal testing (with p-values) between arms will be performed.

A sensitivity analysis will be performed based on the parent's phone call. On each follow-up phone call, the question "Since we last spoke, did your child experience any significant asthma events" is asked. The following options are available for the parent to select:

- Hospitalization with overnight stay
- Emergency department visit
- Unscheduled visit to urgent care clinic or a healthcare provider
- Used oral corticosteroids
- Experienced oral thrush

ED-recidivism will be captured at each of the three follow-up phone calls. In the sensitivity analysis, we will categorize each subject as observing ED-recidivism if the option "Emergency department visit" is selected for any of the follow-up periods. Individuals who mark 'Don't know/don't remember' to the response will not be included in the summaries. The rate for each arm, exact binomial 95% confidence interval for each arm, as well as the the difference in proportions will be summarized for the sensitivity analysis in a similar fashion as the primary statistical analysis mentioned above.

7.3.2 Preliminary Cost-Effectiveness Analysis of Treatment

The DCC biostatisticians will provide the data necessary to perform a cost effectiveness analysis to the PIs of the study. These data will be summarized as follows (Table 2):

Variable	Overall	Arm	
		ED Prescribing	ED Dispensing with School Supervision
ED Visits	XX% (CI)	XX% (CI)	XX% (CI)
Hospitalization	XX% (CI)	XX% (CI)	XX% (CI)
Unscheduled visit to urgent care clinic or healthcare provider	XX% (CI)	XX% (CI)	XX% (CI)
Albuterol Medication Fill			
30 Day Phone Call	—	XX% (CI)	—
60 Day Phone Call	—	XX% (CI)	—
90 Day Phone Call	—	XX% (CI)	—
Budesonide Medication Fill			
30 Day Phone Call	—	XX% (CI)	—
60 Day Phone Call	—	XX% (CI)	—
90 Day Phone Call	—	XX% (CI)	—
Seen by Asthma Specialist			
30 Day Phone Call	XX% (CI)	XX% (CI)	XX% (CI)
60 Day Phone Call	XX% (CI)	XX% (CI)	XX% (CI)
90 Day Phone Call	XX% (CI)	XX% (CI)	XX% (CI)
Seen by Primary Care Provider			
30 Day Phone Call	XX% (CI)	XX% (CI)	XX% (CI)
60 Day Phone Call	XX% (CI)	XX% (CI)	XX% (CI)
90 Day Phone Call	XX% (CI)	XX% (CI)	XX% (CI)
Symptom-Free Days Average of Child-specific Proportions	XX% (CI)	XX% (CI)	XX% (CI)
Symptom Free Days Overall Proportion	XX%	XX%	XX%

Table 2: Cost effectiveness variables

For each Confidence Interval (CI) in the table above, except Symptom-Free Days Average of Child-specific Proportions, the exact binomial distribution will be used to compute the 95% confidence interval. For Symptom-Free Days Average of Child-specific Proportions, the typical 95% interval around continuous values will be used. The following definitions will be used for each variable:

ED Visits

ED visits will be counted as a 'YES' if the subject has a documented (through the EHR) visit to the ED due to asthma within 90 days of randomization. All other situations (including the scenarios where the parent reports an ED visit but there is no documented ED visit in the EHR) will be counted as a 'NO'.

Hospitalizations

Hospitalizations will be counted as a 'YES' if the subject has a documented (through the EHR) hospitalization to the ED due to asthma within 90 days of randomization. All other situations (including the scenarios where the parent reports a hospitalization but there is no documented hospitalization in the EHR) will be counted as a 'NO'.

Other Urgent Care Provider

The parents are asked the question: "Since we last spoke, did your child experience any of these asthma related events?" at each visit. If the option 'Unscheduled visit to urgent care clinic or a healthcare provider' is checked, then the individual will be marked as 'YES' for other urgent care provider visits. All other scenarios will be considered a 'NO'unless the response is 'Don't know/don't remember'. The don't know/don't remember will not be included in the proportion calculation.

Medication Fills

At each follow-up phone call, the parents in the ED-prescribing arm are asked if they filled the child's medication for either albuterol or budesonide. The proportions of 'YES' answers will be summarized by time point out of the non-missing responses. The responses are not cumulative (i.e., each questionnaire will focus solely on the time period since last contact, instead of looking at 'ever filled').

Healthcare Follow-ups

At each follow-up phone call, the parents are asked if their child has been seen by a healthcare provider for follow-up care of their asthma. Two of the options if they say yes are Asthma Specialist and Primary Care Provider. The proportions of 'YES' answers will be summarized by time point out of the non-missing responses. If a parent says 'no' to their child being seen by a healthcare provider, both the Asthma Specialist and the Primary Care Provider will be marked no.

Symptom-Free Days Average of Child-specific Proportion

For each arm, 21 texts will be sent out to the parents of the children (7 texts each month) asking about the asthma symptoms for the previous 24 hours. We will consider the child to have a symptom-free day if no symptoms were reported that day. For each child, the proportion of symptom-free days will be calculated. Missing values will not be used in the calculation. For example, if the parents respond to 15 of the 21 texts, and 10 of the 15 responses indicated that the child did not have symptoms that day, then the proportion of symptom-free days for that child would be $\frac{10}{15} = 66\%$. The proportion is calculated for each child and the average of the child-specific proportions are reported.

Symptom-Free Days Overall Proportion
As mentioned in the previous paragraph, we will have the number of symptom-free days out of the total number of responses provided from the parents. For each arm, we will produce an overall fraction by summing the total number of symptom-free days in the numerator and the total number of text responses in the denominator. For example, if we have three children and child one had 16 out of 20 symptom-free days, child two had 19 out of 21 symptom-free days, and child three had 12 out of 15 symptom-free days, then the symptom-free days overall proportion would be $\frac{16+19+12}{20+21+15} = 84\%$.

7.4 Technical Approaches for Subgroup Analyses

The subgroups of interest are:

- Ethnicity
- Race
- Age
- Gender
- BMI

Ethnicity will be categorized as Hispanic or Latino vs not Hispanic nor Latino. Race will be categorized as white, black, or other. Age will be categorized as 6-8 (i.e., <9) years of age at the time of randomization vs 9-12 years of age at the time of randomization. BMI will use the traditional classifications (<25.0: Underweight/normal, 25-29.9: overweight, ≥30: obese).

The overall score for parent satisfaction (i.e., average of the Likert responses) will be summarized through descriptive statistics (mean, SD) by the various subgroups. ED-recidivism within 90 days will be summarized with frequency counts and percentages by the various subgroups and arm. If any observed subgroup has a small sample size (<5 in any subgroup), then the subgroup specific proportions will not be presented. In the case of Race, 'Other' would be combined with 'Black' if either race has a small sample size.

7.5 Safety Analyses

There are no formal safety outcomes for ED-SAMS that are not captured by the primary and secondary outcomes.

7.5.1 Adverse Events

Adverse Events (AEs) will be recorded from the time of randomization through 120 days after randomization. Symptoms/side-effects described previously will generally not be counted as AEs, as they are reported separately. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0, or newer.

Serious Adverse Events/Death Serious adverse events (SAEs) will be reported from randomization through 120 days after randomization. SAEs/Deaths will be reported in a similar fashion to the more general AE reports. In addition, narratives will be available for each event.

7.5.2 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.

8 SAMPLE SIZE DETERMINATION

Randomization of 90 subjects allows estimation of consent and acceptance 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%.

The consent and approach rates will be estimated using numerators of at least 90 (because 90 subjects will be randomized). The number consenting and the number approached must be at least as large as the number randomized. The margin of error for a sample proportion, X/N, can be calculated through the equation $1.96 * \sqrt{\frac{(X/N)*(1-X/N)}{N}}$, assuming a normal approximation (and that N was fixed in advance). This assumption is violated, but it provides an approximation to the standard error. For any given value of X, the maximum margin of error according to this formula can be determined as a function of N. If X is 90, the margin of error would be maximized with $N = 135$, which yields a margin of error of 0.0795, or 7.95%; see Figure 1. If X is greater than 90, the N that maximizes the margin of error will change but the maximum possible margin of error would decrease in relation to the aforementioned 7.95%.

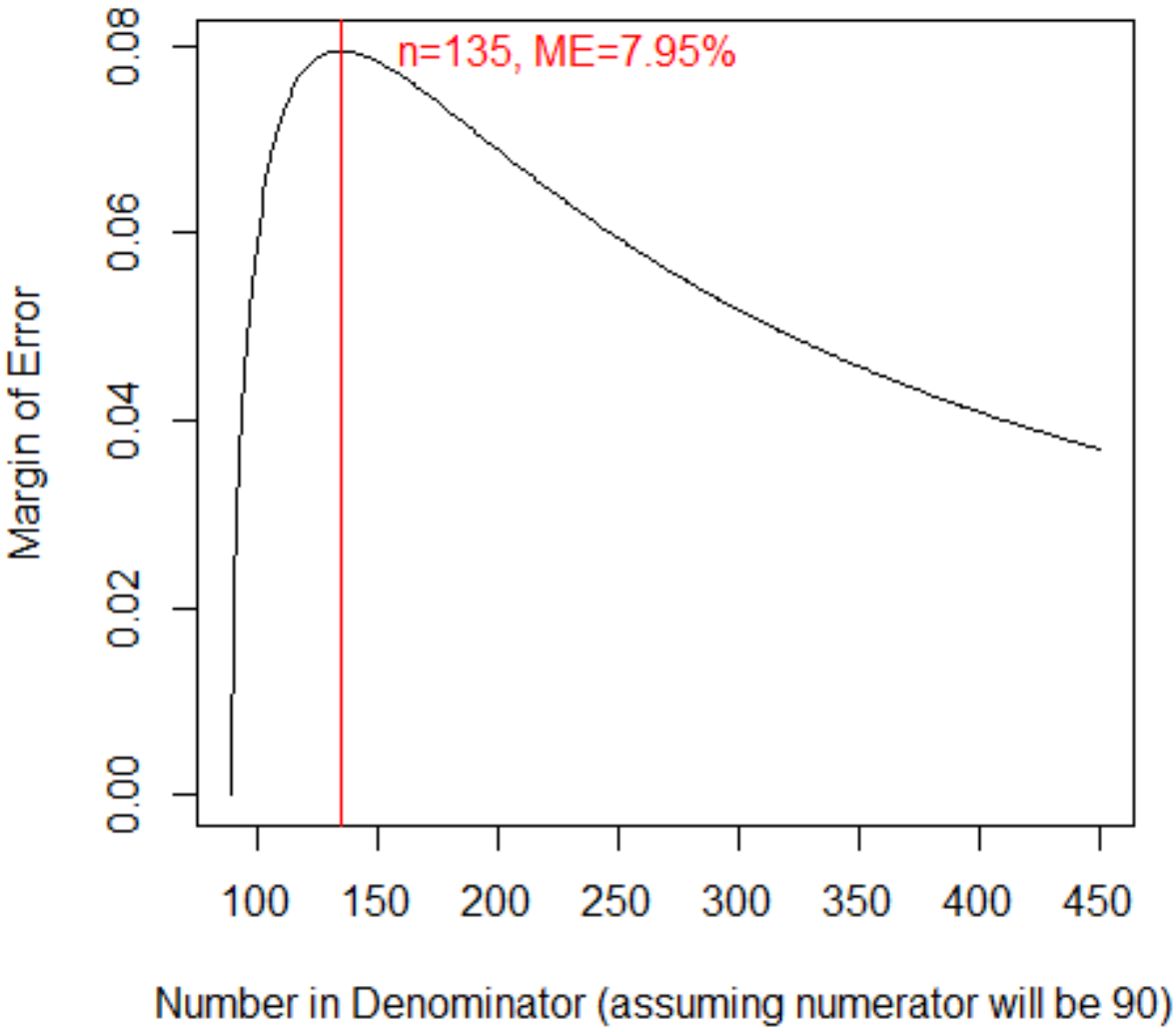

Figure 1: Possible margin of errors as a function of the numerator (number of those approached for consent or number approached for acceptance) assuming the numerator of proportion is 90

For the recidivism rates, assuming that the denominator N is 45 for each arm, the margin of error would be maximized with $X = 22$ or $X = 23$, each of which yields the same maximal margin of error of 14.6% (if using the normal approximation). If data are missing, the values may be slightly larger.

9 References