Statistical Analysis Plan

Protocol Title (Number): Procalcitonin to Reduce Antibiotic Use in Pediatric Pneumonia (047)

Protocol Version and Date: 1.04; September 17, 2021

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

SAP Version and Date: 1.00; October 5, 2021

SAP Version 1 Date: October 5, 2021

CONFIDENTIAL

Approvals:

Approved By:

Name	Title	Date
Name	Title	Date

Contents

Abbreviations . . . vi

1 PREFACE **1**
1.1 Purpose of SAP . . . 1
1.2 Auxiliary/Other Documents . . . 1

2 STUDY OBJECTIVES AND OUTCOMES **1**
2.1 Study Objectives . . . 1
2.1.1 Primary Objective(s) . . . 1
2.2 Study Outcomes . . . 2
2.2.1 Primary Outcome(s) . . . 2
2.2.2 Secondary Outcome(s) . . . 2
[redacted]
2.2.4 Safety Outcome(s) . . . 3

3 STUDY DESIGN AND METHODS **3**
3.1 Overall Study Design . . . 3
3.2 Method of Treatment Assignment and Randomization . . . 3
3.2.1 Delivery of Randomization and Emergency Backup . . . 4
3.3 Treatment Masking (Blinding) . . . 4

4 STUDY SUBJECTS AND ANALYSIS POPULATIONS **4**
4.1 Eligibility . . . 4
4.2 Populations for Analyses . . . 4
4.2.1 Screening Population . . . 4
4.2.2 Study Eligible Population . . . 5
4.2.3 Stage I Approached Population . . . 5
4.2.4 Stage I Consented Population . . . 5
4.2.5 Blood Draw Population . . . 5
4.2.6 RCT Eligible Population . . . 5
4.2.7 Stage II Approached Population . . . 5
4.2.8 Stage II Consented Population . . . 5
4.2.9 Intention-to-Treat Population . . . 5
4.2.10 Safety Population . . . 6

5 GENERAL ISSUES FOR STATISTICAL ANALYSES **6**
5.1 Analysis Software . . . 6
5.2 Methods for Withdrawals, Missing Data, and Outliers . . . 6
5.3 Multiple Comparisons and Multiplicity . . . 6

5.4 Planned Subgroups, Interactions, and Covariates . . . 6
5.5 Derived and Computed Variables . . . 7
5.5.1 Enrollment Rates . . . 7
5.5.2 Consent Rate between Stage I and Stage II . . . 7
5.5.3 Feasibility and Usability of Video Chat Follow-Up . . . 7
5.5.4 Lost to Follow-up Rates . . . 7
[redacted]
5.5.6 Clinic or ED Visits . . . 8
5.5.7 Hospitalization . . . 9
[redacted]
5.5.9 Adverse Events . . . 10
[redacted]
5.5.13 Frequency and Types of Adverse Events . . . 14
[redacted]
5.6 Independent Review . . . 15

6 INTERIM ANALYSES **15**
6.1 Frequency of and Timepoints for Interim Analysis . . . 15
6.2 Stopping Rules for Interim Efficacy Analysis . . . 15
6.3 Futility Monitoring in the Interim Analysis . . . 15
6.4 Subgroups in the Interim Analysis . . . 16

7 PLANNED ANALYSES **16**
7.1 Description of Subject Characteristics . . . 16
7.2 Primary Outcome Analysis . . . 16
7.3 Secondary Outcome(s) Analyses . . . 16
7.3.1 Consent and drop-out rates between the two stages of consent . . . 16
7.3.2 Parental attitudes and beliefs about trial procedures . . . 16
7.3.3 Feasibility and usability of video chat follow-up . . . 16
7.3.4 Lost to follow-up rates . . . 17
[redacted]

8 SAMPLE SIZE DETERMINATION **18**

9 References **18**

Abbreviations

Abbreviation	Definition
BLOOD DRAW	Blood Draw Population
CAP	Community Acquired Pneumonia
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DOOR	Desirability of Outcome Ranking
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
ELIGIBLE	Eligible Population
ITT	Intent-To-Treat Population
PCT	Procalcitonin
RADAR	Response-Adjusted Duration of Antibiotic Risk
RCT ELIGIBLE	RCT Eligible Population
(S)AE	(Serious) Adverse Event
SAFETY	Safety Population
SCREEN	Screening Population
SAP	Statistical Analysis Plan
STAGE I APPROACHED	Stage I Approached Population
STAGE I CONSENTED	Stage I Consented Population
STAGE II APPROACHED	Stage II Approached Population
STAGE II CONSENTED	Stage II Consented Population

1 PREFACE

1.1 Purpose of SAP

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the protocol: Procalcitonin to Reduce Antibiotic Use in Pediatric Pneumonia (P-RAPP).

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: Procalcitonin to Reduce Antibiotic Use in Pediatric Pneumonia.
- Case Report Forms (CRFs) for the P-RAPP 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 P-RAPP 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 objective of the P-RAPP trial is to demonstrate the feasibility to efficiently and effectively enroll low-risk children with Community Acquired Pneumonia (CAP) and

Procalcitonin (PCT) levels < 0.25 into a multicenter randomized controlled trial evaluating antibiotics vs placebo, while refining study procedures for the subsequent large clinical trial.

2.2 Study Outcomes

2.2.1 Primary Outcome(s)

The primary outcome in this pilot study is the enrollment rate per site per month.

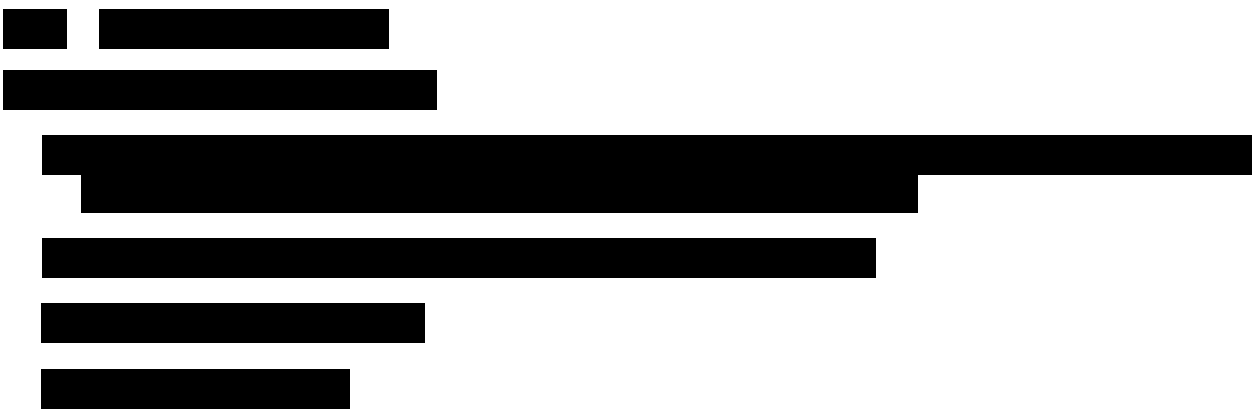
Eligibility for Primary Analysis The enrollment rate will be derived for those subjects who are randomized into the second stage of the trial.

2.2.2 Secondary Outcome(s)

Secondary outcomes of this pilot study include:

1. Consent and drop-out rates between the two stages of consent
2. Parental attitudes and beliefs about trial procedures
3. Feasibility and usability of video chat follow-up
4. Lost to follow-up rates

Eligibility for Secondary Analysis Secondary outcome 1 will include all patients who have a PCT < 0.25 from Stage I of the trial. Secondary outcome 2 will be analyzed through interview data which are collected separate from the clinical trial. Secondary outcomes 3 and 4 will be analyzed among those subjects who are randomized into Stage II of the trial.



[redacted]

2.2.4 Safety Outcome(s)

There are no pre-specified safety outcomes. Several exploratory outcomes capture safety events.

3 STUDY DESIGN AND METHODS

3.1 Overall Study Design

This pilot clinical trial is a 3-site, randomized, placebo-controlled, double-blinded trial. There are two stages of enrollment in this study. The first stage (Stage I) will collect data on any eligible and consented subject. Blood will be collected on these subjects in Stage I and the subjects PCT will be evaluated. If the PCT is less than 0.25 ng/mL, then the subject will be approached for consent to participate in the RCT (Stage II). If the subject is consented for Stage II, randomization is performed and the subject is enrolled into the clinical trial. Randomized subjects will be followed daily for 7 days. At 7 and 21 days after the ED visit, a follow-up phone/video call will be made to assess further outcomes for randomized subjects. After 21 days, a medical chart review will be performed to assess additional outcomes on all subjects in both Stage I and Stage II.

3.2 Method of Treatment Assignment and Randomization

After enrollment and confirmation of a PCT $<$0.25 ng/mL, subjects will be randomized to a 7-day course of either amoxicillin or placebo. Randomization will be stratified at a 1:1 ratio stratified by site with block sizes of 2 and 4.

3.2.1 Delivery of Randomization and Emergency Backup

Randomization will occur within the database. There are no emergency backup envelopes for this study. The randomization process will produce a randomization ID which the site coordinator will then provide to the site pharmacist (who will have a mechanism to identify arm and produce study drug).

3.3 Treatment Masking (Blinding)

The P-RAPP trial will be performed in a double-blind fashion. All study personnel, including investigators and research coordinators, shall be blinded to assigned treatment arm for each enrolled subject. Of necessity, biostatisticians involved in presenting interim analyses to the DSMB will be aware which subjects have received which arm due to the derivation of some outcomes.

Unblinded personnel in this study will include: the site research pharmacist and, possibly, a pharmacy monitor contracted by the DCC expressly for the purpose of ensuring assigned treatments have been correctly prepared and delivered in this study. The DSMB may request to be unblinded to treatment assignment at any time. If this occurs, the DCC biostatisticians will also be unblinded.

4 STUDY SUBJECTS AND ANALYSIS POPULATIONS

4.1 Eligibility

Study eligibility details can be found in the protocol.

4.2 Populations for Analyses

There are several populations considered for analyses. These are described in detail below.

4.2.1 Screening Population

The screening population (SCREEN) includes all subjects who are screened for eligibility into the trial, regardless of whether or not they are approached for consent for Stage I. This population represents all patients who meet inclusion criteria outlined in the study protocol. This population will be used for reporting of study flow per Consolidated Standards of Reporting Trials (CONSORT) guidelines.

4.2.2 Study Eligible Population

The study eligible population (ELIGIBLE) includes all SCREEN subjects who meet study inclusion/exclusion criteria (regardless of whether they consent in Stage I).

4.2.3 Stage I Approached Population

The Stage I approached population (STAGE I APPROACHED) includes all ELIGIBLE subjects who were approached by a study team member to participate in the study.

4.2.4 Stage I Consented Population

The Stage I consented population (STAGE I CONSENTED) includes all STAGE I APPROACHED subjects who have consented to get their blood draw.

4.2.5 Blood Draw Population

The blood draw population (BLOOD DRAW) includes all STAGE I CONSENTED who have a blood draw obtained to evaluate PCT.

4.2.6 RCT Eligible Population

The RCT eligible population (RCT ELIGIBLE) includes all BLOOD DRAW subjects whose PCT value is <0.25 ng/mL.

4.2.7 Stage II Approached Population

The Stage II approached population (STAGE II APPROACHED) includes all RCT ELIGIBLE subjects who were approached by a study team member to participate in the RCT.

4.2.8 Stage II Consented Population

The Stage II consented population (STAGE II CONSENTED) includes all STAGE II APPROACHED subjects who have consented to participate in the RCT.

4.2.9 Intention-to-Treat Population

The Intention-to-Treat (ITT) population includes all subjects who are randomized into the trial, regardless of adherence to the protocol, including, for example, subjects who receive no study drug. The ITT population will be used for all exploratory outcome analyses where differences are evaluated between arms. All analyses using the ITT population

will be based on each subject's assigned treatment arm, regardless of treatment actually received.

4.2.10 Safety Population

The safety population (SAFETY) includes all subjects who receive any study drug. Reporting of results based on this population will be summarized according to treatment received. This population will be used for analysis of adverse events.

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 and StatXact®, may be used for particular specialized procedures.

5.2 Methods for Withdrawals, Missing Data, and Outliers

Per the intention-to-treat principle, subjects who withdraw from the study or are lost to follow-up will have all available data used in the analysis. In the event that a substantial number of subjects are withdrawn or lost to follow-up, baseline characteristics and available information on hospital course will be reviewed and compared to subjects not withdrawn or lost, to assess empirically if these subjects differ from those remaining in the study for the scheduled treatment and follow-up time.

Outliers will be reviewed for validity. Outliers that are valid, for example, high number of vomiting episodes, will be included in all primary reports from this trial.

Due to this being a pilot study, missing data will remain missing instead of being imputed.

5.3 Multiple Comparisons and Multiplicity

As this is a pilot study, no adjustments will be made for multiple comparisons. It will be noted that no adjustments were made in any manuscript that publishes data from this pilot study.

5.4 Planned Subgroups, Interactions, and Covariates

There are no subgroup analyses planned for this pilot study.

5.5 Derived and Computed Variables

5.5.1 Enrollment Rates

The enrollment rate will be calculated as the number of subjects in the ITT population divided by the total time all sites were open for enrollment. The time (in months summarized as continuous) will be computed for each site based on the site's activation date and the site's closure date. The sum of all of these individual times is used to calculate the total time all sites were open for enrollment.

5.5.2 Consent Rate between Stage I and Stage II

The consent rate (which is 100% minus the dropout rate) will be calculated as the ratio of STAGE II CONSENTED and RCT ELIGIBLE (summarized as a proportion).

5.5.3 Feasibility and Usability of Video Chat Follow-Up

Secondary outcomes 3 and 4 will be analyzed among those subjects who are randomized into Stage II of the trial. On the Day 7 follow-up visit, we record the type of device used to conduct the visit. If the device is 'Mobile Phone (phone call)', then the visit will be categorized as a phone visit. If the type of device is 'Mobile Phone (video)', 'Tablet', 'Laptop', or 'Desktop computer', then the visit will be categorized as a video visit. The proportion of video visits out of all Day 7 follow-up visits will be computed. Subjects without a Day 7 visit (i.e., missed the Day 7 follow-up) will not be included in the denominator.

Among the subjects who are categorized as a video follow-up, we will also summarize the proportion of subjects where the entire assessment was able to be completed using video follow-up. Among those subjects who are categorized as a video follow-up but WERE NOT able to be completed, we will summarize the reasons why with frequencies and percentages. Among those subjects who are categorized as a video follow-up and WERE able to be completed, we will summarize the experience of the calls (video quality, sound quality, ease of use, overall experience) using frequencies and percentages. Categories of these experiences may be combined when summarizing results (e.g., combine Very Negative with Negative in a summary).

5.5.4 Lost to Follow-up Rates

The primary lost to follow-up rate will be summarized for the Day 7 follow-up. A subject will be categorized as having a Day 7 follow-up if the Date of Day 7 Follow-up is not miss-

ing (regardless if the date is within the 7-day window). If the date is missing, the subject will be categorized as missing the Day 7 follow-up. The rate of Day 7 follow-ups will be summarized as a proportion. A similar analysis will be done for the Day 21 follow-up.

For the daily assessments, we will calculate whether the subject completed at least five out of the six possible daily assessments. The proportion of subjects who completed at least five assessments will be summarized.

5.5.6 Clinic or ED Visits

Two definitions of clinic or ED visits will be derived. These are described in the following paragraphs:

Any Visit A subject will be categorized as having seen a provider if the subject indicates that they have seen a doctor (in the ED or primary care provider) since the study ED visit on the Day 7 follow-up (regardless of whether it is planned or unplanned).

Unplanned Visit A subject will be categorized as having seen a provider if the subject indicates that they have seen a doctor (in the ED or primary care provider) since the study ED visit on the Day 7 follow-up (only an unplanned study visit for a non-ED visit).

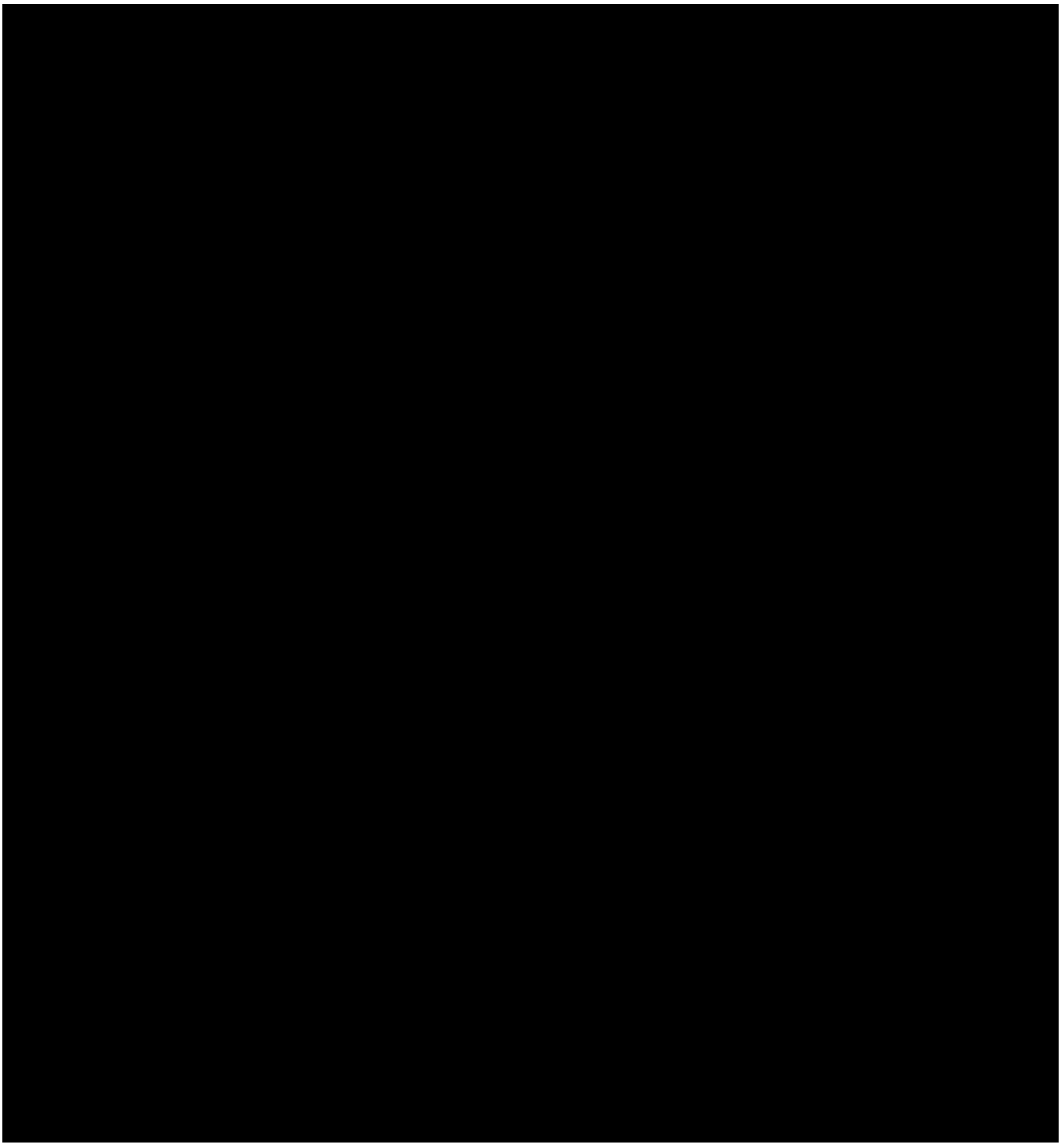
The proportions of subjects for the two definitions above will be summarized out of the proportion of subjects with a Day 7 follow-up visit (categorized as having a Day 7 follow-up if the Date of Day 7 Follow-up is not missing). A repeat of these two summaries will be performed for the Day 21 follow-up visit.

5.5.7 Hospitalization

A subject will be categorized as having been hospitalized if the subject indicates that they were hospitalized since the study ED visit on the Day 7 follow-up. The proportion of subjects who were hospitalized will be summarized out of the proportion of subjects with a Day 7 follow-up visit (categorized as having a Day 7 follow-up if the Date of Day 7 Follow-up is not missing). A repeat of this summary will be performed for the Day 21 follow-up visit.

5.5.9 Adverse Events

Adverse events will be captured through the daily assessments. On the daily log and on Day 7, we ask about several symptoms. On any daily assessment or Day 7, whatever the worst category reported across the week is the category assigned to the subject. For example, on the first day following the ED visit, if the parent reports the child had 4+ episodes of vomiting that day, then the child will be categorized as 'Severe' AEs regardless of how quickly they might improve the remaining part of the week. Allergic reactions is captured as 'rash', stomatitis is captured as 'had any ulcers in the mouth', and candidiasis is captured as 'had any white patches in the mouth or a rash in the groin region'. The categorization of mild, moderate, and severe can be seen in Figure 1.



[redacted]

[redacted]

5.5.13 Frequency and Types of Adverse Events

For each of the adverse events summarized in Figure 1, we will categorize each subject as whether or not the AE was observed based on:

- the daily assessments
- the Day 7 survey

If the subject experiences the AE at any reported period, the subject will be labeled as having experienced the AE. If the subject has at least one assessment completed (either daily or Day 7) and all observed assessments do not indicate the AE occurring, the subject will be labeled as not experiencing the AE.

5.6 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 is a pilot study evaluating the feasibility of the trial so no formal interim analyses will be performed. The DSMB will meet prior to study start and then once study is completed. If enrollment is anticipated to go longer than 8 months, then the DSMB will have the option to meet to perform a safety review of the data.

6.2 Stopping Rules for Interim Efficacy Analysis

There is no formal efficacy monitoring in this pilot study.

6.3 Futility Monitoring in the Interim Analysis

There is no formal futility monitoring in this pilot study.

6.4 Subgroups in the Interim Analysis

There are no formal pre-specified subgroups of interest in this pilot study that will be evaluated due to the small number of enrollments.

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

- gender
- race
- age
- ethnicity

7.2 Primary Outcome Analysis

The primary outcome, enrollment rate, and the 95% confidence interval around the enrollment rate will be summarized overall.

7.3 Secondary Outcome(s) Analyses

7.3.1 Consent and drop-out rates between the two stages of consent

The consent rate between Stage I and Stage II (summarized as a proportion) and exact 95% confidence interval of the proportion will be reported.

7.3.2 Parental attitudes and beliefs about trial procedures

Parental attitudes and beliefs about trial procedures will be evaluated outside of the clinical trial. Qualitative analyses will be performed by the lead investigator and his team and details are not discussed in this SAP.

7.3.3 Feasibility and usability of video chat follow-up

The video follow-up rate and entire assessment completed through video (summarized as a proportions) and exact 95% confidence intervals of the proportions will be reported.

7.3.4 Lost to follow-up rates

Lost to follow-up rates (summarized as a proportions) and exact 95% confidence intervals of the proportions will be reported.

8 SAMPLE SIZE DETERMINATION

We are seeking to enroll and randomize 2 children per site per month as part of this pilot trial. Using 40% as an estimate of children enrolled in Stage I being eligible for Stage II (PCT $<$0.25), we anticipate that we will need to obtain PCT and baseline data from 5 children per site per month to enroll 2 with PCT $<$0.25 at each site.; Thus, over a 6 month period, we anticipate obtaining baseline data and PCT on 90 children across 3 sites and enrolling 36 of these children into this pilot RCT. As soon as 36 children are enrolled in the RCT, the pilot trial will stop.

9 References