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Statistical Analysis Plan

CRY MANAGEMENT AND AWARENESS TOOL (COOL)
EBB17GC16811_2

Protocol:	EBB17GC16811_2, 2.0

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - SPONSOR

SAP details	
Study title:	CRY MANAGEMENT AND AWARENESS TOOL (COOL)
Study:	COOL study, EBB17GC16811_2
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SAP approved by the sponsor:
We, the undersigned, have reviewed and approved this SAP including the appendices.

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TABLE OF CONTENTS

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ABBREVIATIONS AND DEFINITIONS

Acronyms	Full form
AE	Adverse event
CI	Confidence Interval
COOL	**C**ry management and awareness t**ool**
HCP	Health Care Provider
LENA	Language ENvironment Analysis
PI	Principal Investigator
SAP	Statistical Analysis Plan
SBCC	Singapore Baby and Child Clinic

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses which will be provided on the study, in agreement with the version 2.0 of protocol dated the 07-03-2019, the version 2.2 of CRF (dated 11-03-2019) and the V2.0 of questionnaire for primary caregiver (dated 11-Mar-2019). This SAP is a detailed explanation and extension of the statistical analyses pre-planned in the protocol. In case of any deviations, this SAP overrules the protocol, but these modifications will be clearly described in this document. Any additional post-hoc analyses (not included in this SAP) will be distinctly identified in the study report.

The study report including statistical and clinical results will be written in the English language (UK) and presented using Microsoft PowerPoint Slides. For the documentation of statistical methods, the analyses and the results, this report will have to take into account all analyses defined in this SAP and will also mention details of deviation (if any) from SAP during analysis.

2 DESCRIPTION OF STUDY

2.1 Study objectives

2.1.1 Primary study objective

- To evaluate the real-life usability and relevance of the cry and fuss clock generated from the LENA system and the level of engagement due to the content on the COOL mobile app by the primary caregiver.

2.1.2 Secondary study objectives

- To evaluate the real-life usability and relevance of a digital platform for infant crying and fussing in the daily practice of the HCPs.

2.1.3 Exploratory study objectives

- To explore crying and fussing duration quantified by the LENA system
- To explore crying and fussing duration perceived by the primary caregiver
- To explore relationship between infant crying and fussing with parameters like heart rate and sleep pattern collected by Fitbit for the primary caregiver
- To explore the relationship between crying captured by Cocoon Cam with crying and fussing quantified by the LENA system.
- To explore relationship between crying captured by the Cocoon Cam with primary caregiver reported crying.
- To explore the relationship between sleep time of the infant captured by Cocoon Cam with primary caregiver reported sleep time.
- To explore feedback from the primary care giver on the data for infant cry and sleep including push notifications in the Cocoon Cam APP
- To measure the data on usage of the Cocoon Cam APP by the primary caregiver
- To explore the usability of Cocoon Cam and data captured by the Cocoon Cam APP for the HCP in their daily practice

2.2 Study design

This is a non-controlled open label single centre study conducted at the Singapore Baby and Child Clinic (SBCC) Gleneagles Medical Centre in Singapore.

Diagram 1: Subjects who are enrolled only with the LENA recorder

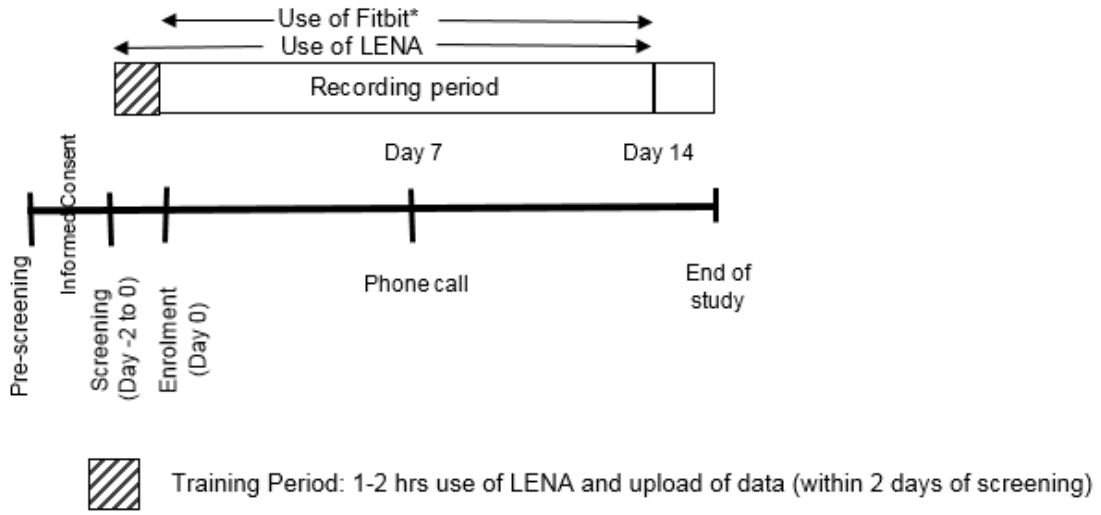
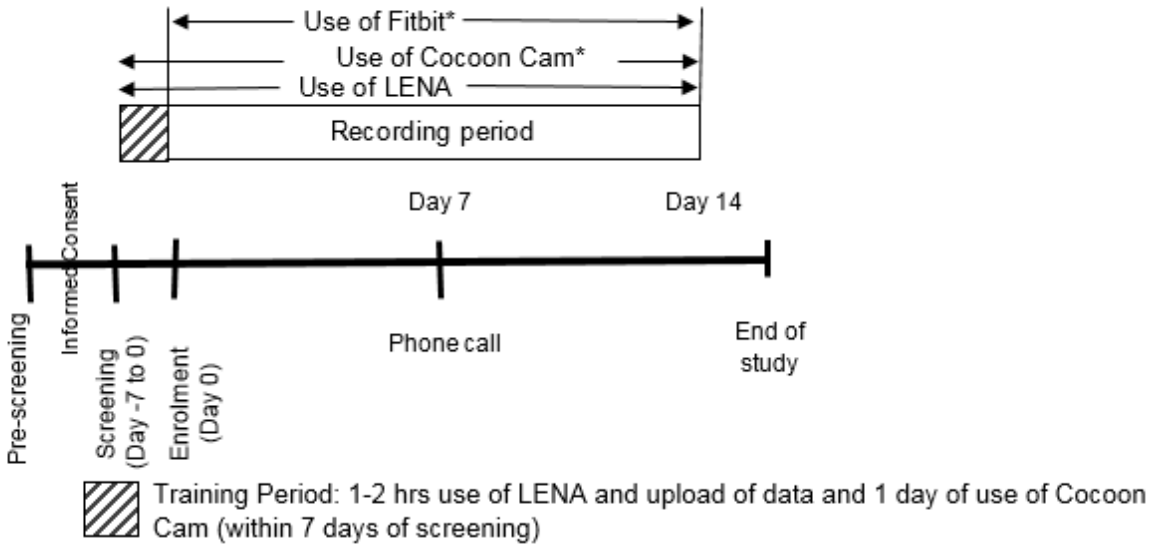


Diagram 2: Subjects who are enrolled with the LENA recorder and Cocoon Cam



The primary caregiver will be provided the LENA recorder kit and in case consented for Fitbit, they will be provided with the Fitbit. For up to five subjects in the study, if the primary caregiver consents for the use of Cocoon Cam they will be provided with the Cocoon Cam kit at screening visit. The subjects Assessment schedule is detailed in Diagram 1 and 2.

Upon enrolling into the study subjects enter a 14 days recording period. During the recording period, the subjects will be using the LENA recorder and those who consented for Fitbit and/or Cocoon Cam will be using the Fitbit and Cocoon Cam respectively. Primary caregiver will complete a daily questionnaire at the end of each day using the COOL mobile app. At the end of 7 days, the site will perform a phone call and the LENA cry and fuss clock generated from the cry and fuss data from the LENA for the recorded

period will be shared with the primary caregiver through the COOL mobile app. After viewing the cry and fuss clock, the primary caregiver will need to complete a questionnaire on the use of LENA recorder and the content of the COOL mobile app. The primary caregiver will continue using the LENA recorder for the next 7 days. At the end of 14 days, the LENA cry and fuss data for the recorded period will be shared with the primary caregiver and the primary caregiver will need to complete another questionnaire on the use and relevance of the cry and fuss clock and overall relevance of the COOL mobile app. For the subjects consented for Cocoon Cam, primary caregiver will need to complete additional questionnaire on daily cry and fuss events and Day 7 and 14 feedback questionnaire. At the end of the recording period, the primary caregiver will schedule an appointment with the PI. If the primary caregiver consents for the use of Fitbit, they will be provided Fitbit to record their parameters like heartrate and sleep pattern through the 14 days after enrolment. At the end of study visit, the primary caregiver will discuss the data provided by the LENA system, the COOL mobile app and Cocoon Cam (if consented) with the PI and PI will use the data to explain to the primary care giver if there is any specific cry pattern that could be assessed based on the objective data from LENA and cry or sleep pattern from the Cocoon Cam (if applicable). The Primary caregiver and PI will complete a questionnaire each post their discussion.

2.3 Inclusion criteria

1. Infants aged 2 to 12 months.
2. Primary caregiver should have reliable access to the internet and a reliable device such as a computer, tablet or smartphone to access the COOL mobile app and able to view the LENA data and complete questionnaires.
3. Primary caregiver should be adequately comfortable in English to read the content in the COOL mobile app and complete questionnaires.
4. Primary caregiver takes care of the child more than 50% of the time

2.4 Exclusion criteria

1. Primary caregiver who is not adequately comfortable in English language to read the content in the COOL mobile app and complete questionnaires.
2. Incapability of the primary caregiver to access COOL mobile app using a reliable device with internet.

2.5 Sample size

Because of the exploratory nature of this study, no formal sample size calculation will be performed. This study plans to have 20 completed subjects. Considering a 20% drop-out rate, approximately 25 subjects are planned to be enrolled.

Assuming a standard deviation of 1.25 for the primary rating score, 20 subjects will achieve a half-width of at most 0.70 for the two-sided 95% confidence interval with a conditional probability of 0.90.

The overall probability of achieving this precision in capturing the true mean is the product of the half-width probability and the confidence level, which is 0.855.

2.6 Study outcome parameters

2.6.1 Primary outcome parameters

The rating by the primary caregivers on the use and relevance of the cry and fuss clock generated from the LENA system data and the rating by the primary caregiver on the level of engagement due to the content on the COOL mobile app.

The primary objective is measured by below variables all measured on a discrete 6-point scale ranging from 0 = not at all to 5 = Yes, very much represent the primary outcome:

- Use and relevance of the LENA recorder and COOL mobile app rated by the primary caregiver at day 14 will be reported (summary statistics)
- Engagement of the LENA recorder and COOL mobile app rated by the primary caregiver at day 14 will be reported (summary statistics)

2.6.2 Secondary outcome parameter

The rating by the HCPs on the use and relevance of data provided by the LENA system in their general practice.
The secondary objective is measured using a rating on a discrete 6-point scale ranging from 0='not at all' to 5='Yes, very much' by the HCPs on the use and relevance of data provided by the LENA system in their general practice.

- Use and relevance of the LENA data in general practice rated by the HCPs at 14 days will be reported (summary statistics)

2.6.3 Exploratory outcome parameter(s)

- Total crying and fussing time captured by the LENA system (continuous variable)
- Crying and fussing time perceived by the parents, discrete variable with 6 categories
  - Less than 10 minutes in a day
  - 10-30 minutes in a day
  - 30 minutes to 1 hour in a day
  - 1 to 2 hours in a day
  - 2 or more hours in a day
  - Don't know
- Parameters recorded by the Fitbit like heart rate and sleep used by the primary caregiver during crying and fussing events registered by LENA system (continuous variables)
- Comments and feedback provided by the primary caregiver on the LENA recorder and the COOL mobile app (free text will be coded as appropriate)
- Comments and feedback provided by the HCP on the LENA recorder and the data provided by LENA system (free text will be coded as appropriate)
- Sleep time recorded by the Cocoon Cam
- Crying time recorded by the Cocoon Cam
- Crying start and end time recorded by the primary caregiver in the COOL app
- Sleep start and end time recorded by the primary caregiver in the COOL app
- Comments and feedback provided by the primary caregiver and HCP on the Cocoon Cam and the activity log for infant cry and sleep including push notifications in the Cocoon Cam app
- Usage data from the Cocoon Cam app

2.6.4 Safety parameter(s)

Incidence, frequency, seriousness, severity and relatedness of AEs related to the study product

2.6.5 Other parameter(s)

- Demographics
  - Sex [male/female]
  - Date of birth of the infant
  - Race and Ethnicity of the infant
- Birth characteristics of the infant (Gestational period, mode of delivery)
- Relevant medical history (including pre-existing conditions)
- Relevant prior medication given to the infant due to medical history
- Relevant medication given to the infant due to any adverse event related to the study product
- Feeding characteristics of the infant

- Household characteristics of the infant (Order of the child in the household, number of siblings, subject and sibling's child care)
- Primary caregiver characteristics (Date of birth, mobile usage, highest level of education, occupational status)
- Subject's Crying pattern history and primary caregiver experience

2.7 Database and data validation

The CRF (Cool web portal), diary and questionnaire data (Cool mobile application) (are collected based on the structure and platform listed in the Server Architecture Document version 1.0. Amazon Web Services (AWS) will be used for creation of hosting environment. Details of the database are as follows: Microsoft SQL Server 2017 (RTM) - 14.0.1000.169 (X64) Copyright (C) 2017 Microsoft Corporation Express Edition (64-bit). Data from LENA recorder is uploaded into the LENA cloud server using an uploader. The reports from the LENA processing are available in the LENA portal for download. The data from the LENA portal are downloaded and transcribed into graphical format using validated programs and uploaded into the Cool mobile application.

CRF, diary and questionnaire data are validated using automated edit checks and data validation steps as described in the Data Validation Plan.

Fitbit data (Sleep and Heart rate) will be exported from Fitabase for analysis at the end of the study.

Cocoon Cam data will be transferred from the Cocoon Cam cloud server and is detailed in Data Transfer Agreement for Cocoon Cam.

2.8 Changes in the conduct of the study compared to protocol

Protocol was amended to extend inclusion criteria to include subjects aged 2 - 12 months and to include Cocoon Cam for up to five subjects, resulting in changes to the exploratory objectives and outcome parameters.

2.9 Unblinding of the study

This is a non-controlled open label single centre study. Blinding is not applicable for this study. The study statistician will have no access to collected data until the SAP has been finalised and signed off.

3 PROTOCOL DEVIATIONS

All protocol deviations will be discussed prior to Database Lock. Possible deviations for this study are:

Description of Deviation	Deviation Type
Visit window deviation	Minor
Not all questionnaires completed	Minor
Enrolled with Cocoon Cam but failed to use Cocoon Cam during the study period	Minor

4 SUBJECTS

4.1 Subject Data Sets

Two subject data sets, "All subjects enrolled (ASE) data set", and "Full-analysis data set" will be used for the analysis. The full-analysis data set will comprise of all enrolled subjects with one post baseline measurement (e.g. at least one measurement from the LENA system is available after enrolment).

4.2 Subjects flowchart

The number and percentage of subjects pre-screened, screened, screen failure, enrolled and full-analysis-set will be provided in consort diagram (Appendix 1).

5 STATISTICAL ANALYSIS

5.1 Interim analysis

Not applicable.

5.2 Final analysis methods

5.2.1 Descriptive summary of baseline parameters

The demographics and other subject characteristics at baseline will be analyzed using the ASE data set and will be reported using standard summary statistics

5.2.2 Statistical approach for primary outcome parameters

The primary analysis will be performed on Full-analysis data set. For primary analysis descriptive statistics will be reported: number of total subjects should be included into the analysis, number of missing observations, number and relative frequency (e.g. percentages) of observations in each rating scale, mean, median, SD, interquartile range, minimum and maximum, 95% confidence interval of population mean.

5.2.3 Statistical approach for secondary outcome parameters

Secondary analysis will be performed on Full-analysis data set. For primary analysis descriptive statistics will be reported: number of total subjects should be included into the analysis, number of missing observations, number and relative frequency (e.g. percentages) of observations in each rating scale, mean, median, SD, interquartile range, minimum and maximum, 95% confidence interval of population mean.

5.2.4 Statistical approach for exploratory outcome parameters except from Fitbit and Cocoon Cam

Exploratory analysis will be performed on Full-analysis data set.
Descriptive analysis for other continuous data:
For each visit, the following descriptive statistics will be reported: number of total subjects should be included into the analysis, number of missing observations, mean, median, standard deviation (SD), interquartile range, minimum and maximum will be reported.

Descriptive analysis for other ordinal and nominal data:
For each visit, the following descriptive statistics will be reported: number of total subjects should be included into the analysis, number of missing observations, number and relative frequency (e.g. percentages) of observations in each class.

The text parameter 'additional elements or features' will be presented as listing by subject.

5.2.5 Statistical approach for exploratory parameters from Fitbit and Cocoon Cam

Analysis of the data from Fitbit and Cocoon Cam will be done as post-hoc analysis.

5.2.6 Statistical approach for other parameters

Descriptive statistics for questionnaire responses will be reported and open text fields will be listed by subject using the ASE data set

Analysis for infants crying and fussing data from Daily Questionnaire:
For daily reported duration and time of crying and fussing, first, number of days the information is reported will be summarized by mean, median, SD, interquartile range, minimum and maximum. Moreover, daily reported duration and time of crying and fussing will be summarized by using number of total person day included, and number and relative frequency (i.e. percentage) in each category will be reported using Full-analysis data set.This will be done as a person day analysis.

The following daily information will be listed in "Subject daily log" based on the daily reported data, category of fussing and crying, total number of episodes of crying and fussing, total time duration in minutes of crying and fussing, total number of episodes of sleeping, total time duration in minutes of sleeping. Moreover, daily total time duration of crying and fussing based on the LENA recorder will be listed too.

Daily total time duration of crying and fussing based on the LENA recorder will be analysed using Full-analysis data set. Mean, median, SD, interquartile range, minimum and maximum will be reported.
Infants' medical history, concomitant condition and adverse event will be analysed using the ASE data set and will be reported using standard descriptive statistics elaborated below.

5.3 Handling of missing data

For outcome parameters, the analysis will be based on the observed data. Missing values will not be imputed.

5.4 Handling multi-centre

Not applicable.

5.5 Handling multiple testing

No correction for multiplicity will be performed as this study is mainly descriptive and no statistical hypothesis testing will be performed.

5.6 Handling visit windows

Not applicable.

5.7 Outlier management

Not applicable.

5.8 General considerations during analysis

- Numeric decimal values will be reported to 3 significant figures.

- Percentage will be calculated using numerator as total number of observations and denominator total number of subjects excluding the missing response. *E.g. For the question "Would you recommend such LENA to your patients?", 14 subjects answered Yes and 2 subjects answered No and for 4 subjects the response is missing, then the percentage for Yes = 87.5 and No = 12.5*
- For calculation of mean, the number of subjects with missing response should also be excluded. E.g.,

Q1.	
Mean	2.5
0	3 (XX.X%)
1	3 (XX.X%)
2	3 (XX.X%)
3	3 (XX.X%)
4	3 (XX.X%)
5	3 (XX.X%)
NMissing	2

5.9 Statistical computer software

All statistical analyses will be carried out using SAS software 9.3 (SAS Institute, Cary, North Carolina, USA).

6 TABLES, LISTINGS AND FIGURES

Details on the tables, listings and figures is described in Appendix 1.

7 ANALYSIS OF STUDY PRODUCT EFFECT

Primary endpoints of usability and relevance is measured on a scale from 0 to 5 with 0 = not at all, 5 = Yes very much, and will be analysed based on the analysis plan described in Section 5.2.2

There is no statistical hypothesis to test as this is a single arm observational study for exploratory purpose only and no confirmatory hypothesis testing will be performed.

8 ANALYSIS OF SAFETY

No medical coding was conducted for this study. All Safety Data (Adverse Events) will be performed on the ASE data set and provided in a listing.

The number (and percentages) of subjects with at least one treatment-emergent (or intervention emergent) adverse event and the number of adverse events (by causality) will be provided overall.

All adverse events and serious adverse events will be summarised in tables and listings.

8.1 Unblinded safety review

Not applicable.

8.2 Exposure to study product

Not applicable

9 EARLY WITHDRAWAL

The number and percentage of subjects with study early withdrawal will be summarized by reason of withdrawal. A listing of study withdrawal subjects will be also displayed. Reason of withdrawal, dates of visits, date of withdrawal, and last visit performed will be presented.

10 QUALITY CHECK/CONTROL OF STATISTICAL ANALYSIS

An independent SAS programmer will be assigned as validator. A separate validation program shall be written for primary (Table 6.1 Primary Outcome Day 14 questionnaire) and secondary parameters (Table 9.1 Secondary Outcome HCP Questionnaire) to compare the output of the original program. For the rest of the items including listings, a visual check of the program and output shall be conducted to ensure accuracy.

11 CHANGES IN THE SAP WITH RESPECT TO THE PROTOCOL

Some textual changes have been done in the objectives to make it clearer.

12 RECORD OF REVISIONS

Version	Date	Nature of Revision
1.0	03-Oct-2019	Document creation

13 REFERENCES

Kumar, P. P. N., Lee, H. C., Bergin, J. (2017, May). Non-Contact Vital Sign Monitor for the NICU. Poster presented at Annual Meeting of Pediatric Academic Societies, San Francisco.

Appendix 1: Tables, Listings and Figures

1. Informed Consent

Table 0: Informed consent

2. Subject demographics and other subject characteristics including medical history /concomitant condition and feeding characteristics at baseline

Table 1: Demographic of infant
Table 2: Primary caregiver's demographic and background
Table 3: Infant and household characteristics
Table 4: Day 0 Questionnaire
Table 5.1: Summary of Feeding Information
Table 5.2: Summary of Feeding Information: Infant / Follow-on formula
This table is populated only for subjects from the ASE who indicated consumption of Infant formula / follow-on formula
Listing 1.1: Feeding Information: Infant / Follow-on formula
This listing is populated only for subjects from the ASE who indicated consumption of Infant formula / follow-on formula
Table 5.3: Summary of Feeding Information: Other beverages, and complementary feeding
This table is populated only for subjects from the ASE who indicated consumption of Other beverages, and/or complementary feeding
Listing 1.2: Other beverages and complementary feeding
Table 5.4: Summary of Complementary Feeding Information
This table is populated only for subjects from the ASE who indicated consumption of complementary feeding

3. Summary of Primary Caregivers' Questionnaires

Table 6.1: Primary outcome (Day 7 and 14)
Table 6.2: Other Questions from Day 7 and 14 Questionnaire
Table 6.3: Summary of Feedback on Cocoon Camera
Table 6.4: Summary on Interest of the product
Listing 2 (2.1 – 2.4): Day 7 Questionnaire: The open text responses will be enlisted in listings
Listing 3 (3.1 – 3.12): Day 14 Questionnaire: The open text responses will be enlisted in listings
Table 7: Summary of post clinic visit questionnaire
Listing 4 (4.1 – 4.3): Post Clinic Visit Questionnaire: The open text responses will be enlisted in listings
Table 8: Summary of daily questionnaire
Listing 5: Primary caregiver feedback

4. Summary of HCP Questionnaire

Table 9.1: Secondary Outcome
Table 9.2: Other Questionnaires
Listing 6 (6.1 to 6.8): The open text responses will be enlisted in listings

5. LENA system data

Table 10: Crying and fussing time by LENA system

6. Diary data and LENA system data

Listing 7: Subject daily log listing for cry, fuss and sleep recorded using diary and LENA System

7. Medical History, Concomitant medication and Adverse event

Table 11: Summary of Medical history and concomitant condition
Listing 8: Medical history and concomitant condition

Listing 9: Concomitant medications
Table 12: Summary of Adverse event
Listing 10 (10.1 to 10.2): Adverse event

8. Early Termination

Table 13: Summary of Early Terminations
Listing 11: Reasons for early termination

9. Subject disposition

Listing 12: Study Population
Listing 13: Subject status
Fig 1: Consort Diagram