# Study Protocol

# CRY MANAGEMENT AND AWARENESS TOOL (COOL)

A proof of concept study to investigate the use and relevance of a digital platform for infant crying and fussing

Version : 2.0
Date : 07-Mar-2019
Protocol number: EBB17GC16811_2

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Version history

| Version | Date | Reason for creating new version | Author |
|---|---|---|---|
| Final 1.0 | 20-Jul-2018 | Document creation | Puspita Roy |
| Final 2.0 | 07-Mar-2019 | Addition of Cocoon Cam as exploratory parameter | Puspita Roy |
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**Ethics Statement**

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

**Confidentiality Statement**

The information provided in this document is the property of Danone Nutricia Research, and is shared with you and your staff in confidence. This information should not be disclosed to others without written authorization from Danone Nutricia Research, except to the extent necessary to ensure adequate conduct of the study.

## PROTOCOL SIGNATURE PAGE - SPONSOR

| **Protocol details** | |
|---|---|
| Study title: | A proof of concept study to investigate the use and relevance of a digital platform for infant crying and fussing |
| Study name/acronym: | COOL |
| Protocol number: | EBB17GC16811_2 |
| Version: | Final version 2.0 |

*Protocol approved by the sponsor:*

We, the undersigned, have reviewed and approved this protocol including the appendices.

| **Senior Team Leader Clinical Research** | Signature | Date |
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| Name | | |

| **Principal Scientist** | Signature | Date |
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| Thomas Ludwig | | 12-03 2019 |
| Name | | |

| **Head of Data Science** | Signature | Date |
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| **Director, Precision Nutrition D-lab** | Signature | Date |
|---|---|---|
| Reshmi Rajendran | | 12/03/2019 |
| Name | | |

## PROTOCOL SIGNATURE PAGE - INVESTIGATOR

*Protocol approved by the Investigator:*
I, the undersigned, have reviewed this protocol including the appendices and I agree to the following:

- To conduct the clinical study in compliance with the protocol, Good Clinical Practice, and any other regulatory requirements.
- To assure that approval for the study is obtained from an Institutional Review Board/ Independent Ethics Committee according to legal requirements, and to comply with their requirements for on-going review and reporting.
- To comply with procedures for data recording and reporting.
- To permit monitoring, auditing and inspection by the sponsor and relevant regulatory agencies.
- To retain study related documents according to regulatory requirements and as agreed with the sponsor.

| | **Investigator** |
|---|---|
| Name: | Dr. Jenny Tang |
| Function: | |
| Signature: | |
| Date: | |

## PROTOCOL SYNOPSIS

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| **Study Title** | A proof of concept study to investigate the use and relevance of a digital platform for infant crying and fussing |
| **Country of Implementation** | Singapore |
| **Study Objectives** | **Primary:** To evaluate the real-life usability and relevance of the cry and fuss clock generated from the LENA recorder data and the level of engagement due to the content on the COOL mobile app by the primary caregiver.<br><br>**Secondary**: To evaluate the real-life usability and relevance of a digital platform for infant crying and fussing in the daily practice of the HCPs.<br><br>**Exploratory:**<br>-To explore crying and fussing duration quantified by LENA recorder<br>-To explore crying and fussing duration perceived by the primary caregiver.<br>-To explore relationship between infant crying and fussing with parameters like heart rate, sleep pattern collected by Fitbit for the primary caregiver.<br>- To explore relationship between crying captured by Cocoon Cam with LENA quantified crying and fussing.<br>- To explore relationship between crying captured by Cocoon Cam with primary caregiver reported crying.<br>- To explore relationship between sleep time captured by Cocoon Cam with primary caregiver reported sleep time.<br>- To explore the real-life usability and relevance of activity log for infant cry and sleep including push notifications in the Cocoon Cam app for the primary care giver<br>- To measure the data on usage of the Cocoon Cam app by the primary caregiver<br>- To explore the usability of Cocoon Cam and data captured by the Cocoon Cam app for the HCP in their daily practice |
| **Study Design** | This is a single centre proof of concept |
| **Study Population** | 20 infants aged 2 to 12 months of age completing the study.<br>Consideration would be made to recruit 10 infants with > 1 hr crying every day and primary caregiver having concern about infant's crying pattern. |
| **Study Duration** | The duration of the study will be approximately 2 weeks for each subject from their primary caregiver(s)/legally acceptable representative(s) signing the informed consent) until completion of end of study questionnaire<br>For Subjects who consent for Cocoon Cam the duration of the study will be approximately 3 weeks, considering additional 1 week for set-up and training period with Cocoon Cam. |
| **Inclusion and Exclusion Criteria** | **Inclusion Criteria:**<br>1. Infants aged 2 to 12 months.<br>2. Primary caregiver should have reliable access to the internet and a reliable device such as a computer, tablet or smartphone to |

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| | access the COOL mobile app and to be able to view the LENA data and complete questionnaires.<br>3. Primary caregiver should be adequately comfortable in English to read the content in the COOL mobile app and complete questionnaires.<br>4. Primary caregiver takes care of the child more than 50% of the time<br><br>**Exclusion Criteria:**<br>1. Primary caregiver who is not adequately comfortable in English language to read the content in the COOL mobile app and complete questionnaires.<br>2. Incapability of the primary caregiver to access COOL mobile app using a reliable device with internet. |
| **End points** | **Primary:** The rating by the primary caregivers on the use and relevance of the cry and fuss clock generated from the LENA recorder data and the rating by the primary caregiver on their level of engagement due to the content on the COOL mobile app<br><br>**Secondary:** The rating by the HCPs on the use and relevance of data provided by the LENA recorder in their general practice<br><br>**Exploratory:**<br>• Total crying and fussing time captured by the LENA recorder<br>• Crying and fussing time perceived by the primary caregiver<br>• Vital parameters like heart rate, sleep recorded by the Fitbit used by the primary caregiver during crying and fussing events registered by LENA<br>• Comments and feedback provided by the primary caregiver on the LENA recorder and the COOL mobile app<br>• Comments and feedback provided by the HCP on the LENA recorder and the data provided<br>• Sleep time recorded by the Cocoon Cam<br>• Crying recorded by the Cocoon Cam<br>• Crying start and end time recorded by the primary caregiver in the COOL app<br>• Sleep start and end time recorded by the primary caregiver in the COOL app<br>• 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<br>• Usage data from the Cocoon Cam app |
| **Study Description** | At screening visit, after parent(s)/guardian(s) of potential subjects and/or legal representatives have been informed about the study, they will be requested to sign the informed consent form (ICF) prior to start of the study. After successful signing of the informed consent, the investigator will assess the eligibility of the subjects. If the subject meets all the inclusion and none of the exclusion criteria, the primary caregiver will complete a detailed questionnaire on subject's demographics, birth, family, feeding characteristics and primary caregiver's characteristics. The primary caregiver will be provided the LENA recorder kit and in case consented for Fitbit, they will be provided with the Fitbit. The primary caregiver will need to complete a training period in order to verify subject's primary caregiver's ability to properly connect, operate and upload data using the LENA |

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| | recorders and uploader. As part of the training period, the primary caregiver will do 1-2 hours of recording using the LENA recorder and successfully upload the data into the LENA cloud server through the internet. Once the study coordinator verifies that the upload is successful, the training and feasibility assessment will be considered as complete and the subject will be considered as enrolled. The primary caregiver of the enrolled subject will be provided access to the COOL mobile app and the recording period will start.<br>During the recording period, the subject will be using the LENA recorder and will complete a daily questionnaire at the end of each day. At the end of 7 days, the site will perform a phone call and the LENA cry and fuss clock generated from the LENA recorder data 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. 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 vital 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 recorder and the COOL mobile app 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. The Primary caregiver and PI will complete a questionnaire each on the use of the data provided by the LENA recorder during their discussion.<br><br>For up to 5 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 primary caregiver will need to complete a training period to verify the ability to properly connect, operate and upload data using the LENA recorders and uploader as well as the Cocoon Cam. As part of the training period, the primary caregiver will have to<br>I) perform 1-2 hours of recording using the LENA recorder<br>II) successfully upload the data into the LENA cloud server through the internet,<br>III) use the Cocoon Cam for 1 day, and<br>IV) be able to start using the Cocoon Cam application.<br><br>Once the study coordinator verifies that the LENA upload is successful and Cocoon Cam set-up is complete, the training and feasibility assessment will be considered as complete and the subject will be considered as enrolled. The primary caregiver of the enrolled subject will be provided access to the COOL mobile app and the recording period will start. During the recording period, in addition to the daily questionnaire, the primary caregiver need to enter cry and sleep time using the COOL app. At the end of 7$^{th}$ day and 14$^{th}$ day, the primary caregiver need to complete questionnaires on the usability of the Cocoon Cam. |
| **Statistical Consideration** | 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. |

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| | 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.<br><br>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. |

## TABLE OF CONTENTS

## ABBREVIATIONS AND DEFINITIONS

| Term | Explanation |
|---|---|
| AE | Adverse events |
| AWS | Amazon Web Server |
| COOL | Cry Management and Awareness Tool |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| eCRF | Electronic Case Report Form |
| EC | Ethics Committee |
| FGIDs | Functional gastrointestinal disorders |
| Fussing | Fussing refers to intermittent distressed vocalisation and has been defined as 'behaviour that is not quite crying but not awake and content either'. |
| HCPs | Healthcare professionals |
| ICF | Informed Consent Form |
| ICH-GCP | International Conference on Harmonisation; Good Clinical Practice |
| IRB | Institutional Review Board |
| ITT | Intention-to-treat |
| LENA | Language **EN**vironment **A**nalysis |
| mITT | Modified intention-to-treat |
| PI | Principal Investigator |
| PP | Per protocol |
| SAE | Serious Adverse Events |
| SUSAR | Suspected unexpected serious adverse reactions |
| US | United States of America |

# 1 INTRODUCTION

Excessive crying and fussing of unknown cause in infants is common and of relevant parental concern. All infants cry but infants who cry a lot have a variety of impacts on parents and health services. On an average, crying peaks at 4-6 weeks of age and then diminishes by 12 weeks of age [1]. In the early months, infants tend to cry most in the late afternoon and evening [2]. Although it is true that babies who cry a lot cry relatively intensely, the majority of their crying is intermittent fussing or fretting, rather than highly intense crying.

Regurgitation, infantile colic and functional constipation are common functional gastrointestinal disorders (FGIDs) during infancy. By providing complete and updated parental education, reassurance and nutritional advice, healthcare professionals can optimise the management of FGIDs and related symptoms and reduce the inappropriate use of medication or dietary interventions [3].

LENA stands for **L**anguage **EN**vironment **A**nalysis and is known as the "talk pedometer" but it provides more than just the counting of child vocalizations, conversational turns, and adult words. LENA system comprises a small digital recorder that fits in specialized clothing worn by a child. LENA provides a non-invasive and an objective method of capturing the natural sound/language environment that a child produces and/or experiences. The LENA system started its development over 10 years ago and is currently the gold standard for automated measurement of home language environments. It is used in more than 300 research institutions around the world and its use has been studied in various language environments [4-5]. It has provided research opportunities and information about vocal characteristics as markers for Autism Spectrum Disorder, early-language environment in the NICU, and assessment of language delays [6-10].

In certain research strategies, the LENA recording can be obtained throughout the day, and the audio data subsequently uploaded by the parent via a secured internet server to a cloud platform for processing (Appendix I). The cloud-based software automatically processes the data and generates metadata. The metadata or reports can be viewed electronically by the authorized users. The metadata can provide useful and quantifiable metrics to the researchers and parents. The LENA cloud-based software uses machine-learning algorithms to automatically process the recording (the audio data). The audio processing defines 8 labels that it applies to the data: to first order, every second of the audio data is labelled with one of these 8 categories – Male Adult, Female Adult, Key Child, Other Child, Overlap, Noise, TV/Electronic, Silence. Only one label applies at any point in time. The key child is the child wearing the LENA recorder. Within the utterances attributed to the key child, the algorithm further subcategories the key child data into vocalization, vegetative and cry period. The cry period can be further stratified into cry and fussiness. The LENA algorithm is validated in a human-rated sample of 124 cry periods from 41 infants and shows 90% sensitivity, 92% specificity, and 91% overall accuracy.

For this study, LENA recorder model# 0121 will be used to record crying and fussing of infants. This study will apply the LENA recorder to detect and quantify episodes of crying and fussing in a small cohort of infants, 2 to 12 months of age. The data collected and interpreted by the LENA system will be summarised in a daily clock and shared with the primary caregiver through a mobile application (mobile app). In addition, the primary caregiver will be provided with insights on infant's crying and fussing patterns in the mobile app. The daily crying and fussing data as interpreted by the LENA will also be shared with the HCP through a web interface. The goal of this study is to investigate the use and relevance of the data generated by the LENA system and insights shared through the mobile application in daily life of the primary caregiver. The study will also evaluate the usability of the objective cry and fuss data provided by the LENA in daily practice of the HCPs. The study will also explore any relation between vital parameters like heart rate, sleep recorded by the Fitbit used by the primary caregiver during crying events registered by LENA. The study will also explore the usability of the Cocoon Cam and its ability to record sleep and cry time for infants.

# 2 STUDY OBJECTIVES

## 2.1 Primary study objective

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

### 2.2 Secondary study objective

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

### 2.3 Exploratory study objective(s)

-To explore crying and fussing duration quantified by LENA recorder
-To explore crying and fussing duration perceived by the primary caregiver
-To explore relationship between infant crying and fussing with parameters like heart rate, sleep pattern collected by Fitbit for the primary caregiver.
- To explore relationship between crying captured by Cocoon Cam with LENA quantified crying and fussing.
- To explore relationship between crying captured by Cocoon Cam with primary caregiver reported crying.
- To explore relationship between sleep time captured by Cocoon Cam with primary caregiver reported sleep time.
- To explore the real-life usability and relevance of activity log for infant cry and sleep including push notifications in the Cocoon Cam APP for the primary care giver
- 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

## 3 STUDY DESIGN

### 3.1 Study design

This is a single centre proof of concept study

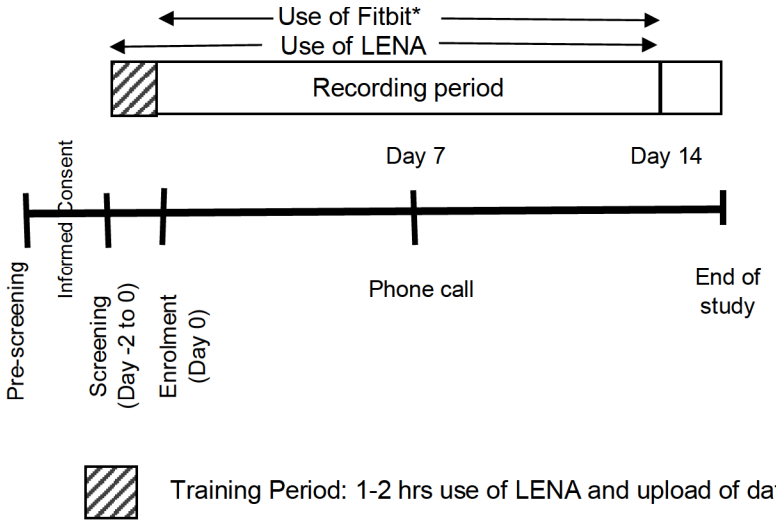
### 3.2 Study description

At screening visit, after parent(s)/ guardian(s) of potential subjects and/or legal representatives have been informed about the study, they will be requested to sign the informed consent form (ICF) prior to start of the study. After successful signing of the informed consent, the investigator will assess the eligibility of the subjects. If the subject meets all the inclusion and none of the exclusion criteria, the primary caregiver will complete a detailed questionnaire on subject's demographics, birth, family, feeding characteristics and primary caregiver's characteristics. The primary caregiver will be provided the LENA recorder kit and in case consented for Fitbit, they will be provided with the Fitbit. The primary caregiver will need to complete a training period in order to verify a subject's primary caregiver's ability to properly connect, operate and upload data using the LENA recorders and uploader. As part of the training period, the primary caregiver will do 1-2 hours of recording using the LENA recorder and successfully upload the data into the LENA cloud server through the internet. Once the study coordinator verifies that the upload is successful, the training and feasibility assessment will be considered as complete and the subject will be considered as enrolled. The primary caregiver of the enrolled subject will be provided access to the COOL mobile app and the recording period will start.
During the recording period, the subject will be using the LENA recorder and will complete a daily questionnaire at the end of each day. At the end of 7 days, the site will perform a phone call and the LENA cry and fuss clock generated from the LENA recorder data 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. 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 vital 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 recorder and the COOL mobile app 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. The Primary caregiver and PI will complete a questionnaire each on the use of the data provided by the LENA recorder during their discussion.
For up to 5 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 primary caregiver will need to complete a training period in order to verify subject's primary caregiver's ability to properly connect, operate and upload data using the LENA recorders and uploader as well as the Cocoon Cam. As part of the training period, the primary caregiver will do 1-2 hours of recording using the LENA recorder and successfully upload the data into the LENA cloud server through the internet and use the Cocoon Cam for 1 day and able to start using the Cocoon Cam application. Once the study coordinator verifies that the LENA upload is successful and Cocoon Cam set-up is complete, the training and feasibility assessment will be considered as complete and the subject will be considered as enrolled. The primary caregiver of the enrolled subject will be provided access to the COOL mobile app and the recording period will start. During the recording period, in addition to the daily questionnaire, the primary caregiver need to enter cry and sleep time using the COOL app. At the end of 7$^{th}$ day and 14$^{th}$ day, the primary caregiver need to complete questionnaire on the usability of the Cocoon Cam.

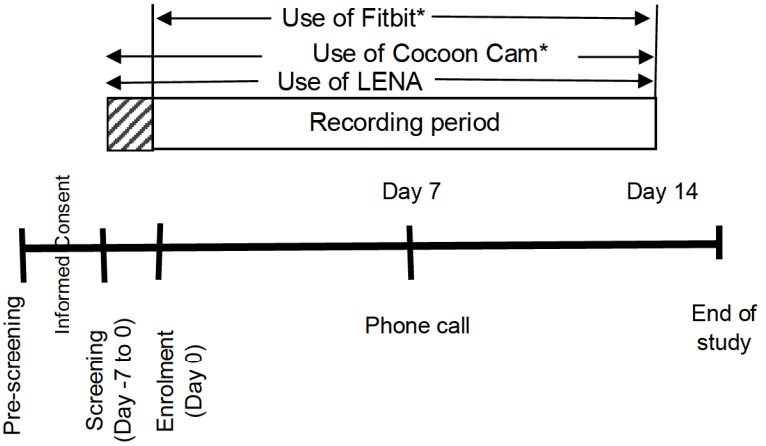
### 3.3 Schematic diagram of study design (*Use of Fitbit and Cocoon Cam is based on Consent given)

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




Training Period: 1-2 hrs use of LENA and upload of data (within 2 days of screening)

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




Training Period: 1-2 hrs use of LENA and upload of data and 1 day of use of Cocoon Cam (within 7 days of screening)

### 3.4 Study Centres

The study will be conducted at the Singapore Baby and Child Clinic(SBCC) Gleneagles Medical Centre in Singapore. Communication with study personnel, including asking questions or reporting of AEs or SAEs will be conducted over the telephone or email messaging as appropriate.

### 3.5 Duration of the study per subject

The duration of the study will be approximately 2 weeks for each subject from their primary caregiver(s)/legally acceptable representative(s) signing the informed consent) until completion of end of study questionnaire

For the subpopulation with Cocoon Cam the duration of the study will be approximately 3 weeks for each subject from their primary caregiver(s)/legally acceptable representative(s) signing the informed consent) until completion of end of study questionnaire.

## 4 SUBJECTS

### 4.1 Study population

20 infants aged 2 to 12 months of age. Consideration would be made to recruit 10 infants with > 1 hr crying every day and primary caregiver having concern about infant's crying pattern.

### 4.2 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

### 4.3 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.

### 4.4 Subject recruitment

Subjects will be approached for participation in the study if they are eligible and interested to take part by their treating physician. To facilitate recruitment, advertisements, posters, social media and/or referral sites may be used.

### 4.5 Instructions and restrictions during the study

There are no restrictions during the study. The primary caregiver will be instructed to perform the study procedures as a part of her regular routine chores.

### 4.6 Subject discontinuation during the study

*4.6.1 Criteria for subject discontinuation*

Infants may be withdrawn from the study at any time (i.e. from any further study procedure, but not from analysis) for the following circumstances:
1) At the primary caregiver's request.
2) If, in the PI's opinion, continuation in the study would be detrimental to the infant's well-being.
3) Poor compliance, as defined at the discretion of the PI (e.g.: a situation in which the primary caregiver does not adhere to the study procedures).

*4.6.2 Procedures in case of subject discontinuation*

Discontinued subjects must be reported to the study monitor. For any subject who discontinues participation before completion of the study protocol, the Investigator must complete the CRF up to the last conducted assessment, the early termination visit pages and the study summary. Whenever feasible, the following information should be documented on the early termination visit pages in the CRF:

- Early termination date
- Reasons for early termination
    - Adverse Event
    - Withdrew informed consent
    - Lost to follow-up
    - Protocol violation
    - Other (to be specified)
- Date and time of study product's last use
- Physical examination (if appropriate)
- Follow-up evaluation/end of study

All data collected until the moment of subject discontinuation will be retained and further used by Danone Nutricia Research. No new data will be collected after the moment of subject discontinuation, except for follow-up of safety data. For subjects who discontinue the study due to the occurrence of (serious) adverse events potentially related to the study procedure, appropriate follow-up will take place until the adverse event has abated, or until a stable situation has been reached, with findings being recorded in the CRF. Alternative medical care of the discontinued subject is to be arranged by the Investigator if necessary.

The study coordinator must make every effort to contact primary caregiver of infants lost to follow-up. Attempts to contact the primary caregiver of infants must be documented in the site record (e.g.: dates and times of attempted telephone/email contact).

Infants whose study participation is terminated prematurely for any of the above listed criteria will be replaced at the PI's discretion.

## 5 STUDY PARAMETERS

### 5.1 Primary outcome parameter

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

### 5.2 Secondary outcome parameter

The rating by the HCPs on the use and relevance of data provided by the LENA recorder in their general practice.

### 5.3 Exploratory outcome parameter(s)

- Total crying and fussing time captured by the LENA recorder
- Crying and fussing time perceived by the primary caregiver
- Vital parameters like heart rate, sleep recorded by the Fitbit used by the primary caregiver during crying and fussing events registered by LENA
- Comments and feedback provided by the primary caregiver on the LENA recorder and the COOL mobile app
- Comments and feedback provided by the HCP on the LENA recorder and the data provided
- 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

### 5.4 Safety parameters

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

### 5.5 Other parameters

#### *5.5.1 Demographics, subject and family characteristics*

Parameters for describing demographics and subject characteristics in this study are:

- 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)

#### *5.5.2 Crying pattern history and primary caregiver experience*

Infant's crying pattern and primary caregiver's experience due to subject's crying and/or fussing for last 7 days before enrolment will be collected through primary caregiver reported questionnaires on the mobile app at enrolment.

The primary caregiver's feedback on the use and relevance of the data provided by the LENA recorder and their feedback on the level of engagement due to the content on the COOL mobile app will be collected through self-reported questionnaires at day 7 and 14.

A daily questionnaire on the average total minutes the subject cried/fussed and the time of the day the subject cried or fussed most based on primary caregiver's perception will be collected for 14 days from enrolment through primary caregiver reported questionnaires on the mobile app.

If the primary caregiver consents for the use of Cocoon Cam, the actual crying, fussing and sleeping time will be recorded by the primary caregiver through daily diary. In addition, the primary caregiver will need to complete a questionnaire on the usability of the Cocoon Cam at Day 7 and 14.

At the end of the study post clinic visit, a questionnaire to understand if the information from the LENA recorder helped to objectively articulate the discussion with the doctor will be collected through primary caregiver reported questionnaires on the mobile app. If the primary caregiver use Cocoon Cam, a feedback from the doctor on the usability of Cocoon Cam will be collected.

#### *5.5.3 HCP Feedback*

At the end of the study post clinic visit, HCP will complete a questionnaire to provide feedback on the usability and relevance of the cry and fuss data generated by the LENA recorder in their daily practice.

#### *5.5.4 Data from Fitbit*

Vital parameters like heart rate and sleep pattern from Fitbit of the primary caregiver.

#### *5.5.5 Data from Cocoon Cam*

Sleep, Crying data captured by Cocoon cam and the usage data for the Cocoon Cam app .

#### *5.5.6 Protocol compliance*

Parameters for assessing protocol compliance in this study are:
- Adherence in answering to the daily questionnaire
- Use of the LENA recorder
- Adherence to the visit window

# 6 STUDY PROCEDURES AND ASSESSMENTS

## 6.1 Procedures per visit

**Screening period:**
At screening visit, after parent(s) / guardian(s) of potential subjects and/or legal representatives have been informed about
the study, they will be requested to sign the informed consent form (ICF) prior to start of the study. After successful signing of the informed consent, the investigator will assess the eligibility of the subjects. If the subject meets all the inclusion and none of the exclusion criteria, the primary caregiver will complete a detailed questionnaire on subject's demographics, family characteristics, household characteristics and feeding characteristics. The primary caregiver will also complete a questionnaire about primary caregiver's characteristics. The primary caregiver will be provided the LENA recorder kit. If the primary caregiver consents for use of Fitbit, the primary caregiver will be provide with the Fitbit. The primary caregiver will be needed to complete a training period in order to verify a subject's primary caregiver's ability to properly connect, operate and upload data using the LENA recorders and uploader. As part of the training period, the primary caregiver will do 1-2 hours of recording using the LENA recorder and successfully upload the data into the LENA cloud server through internet within 2 days of screening. The study coordinator would provide support if the primary caregiver faces any challenges and have any questions. Please note that if the primary caregiver is unable to perform all of the technical prerequisites (after troubleshooting assistance is provided), they will not be able to take part in the trial and will be dismissed as a screen failure, as well as, having to return the LENA recorders and uploader and the Fitbit(if provided). Once the study coordinator verifies that the upload is successful, the training and feasibility assessment will be considered as complete and the subject will be considered as

enrolled. The primary caregiver of the enrolled subject will be provided access to the COOL mobile app and the recording period will start.
For up to 5 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 primary caregiver will need to complete a training period to verify subject's primary caregiver's ability to properly connect, operate and upload data using the LENA recorders and uploader as well as the Cocoon Cam. As part of the training period, the primary caregiver will do 1-2 hours of recording using the LENA recorder and successfully upload the data into the LENA cloud server through the internet and use the Cocoon Cam for 1 day and able to start using the Cocoon Cam application. Once the study coordinator verifies that the LENA upload is successful and Cocoon Cam set-up is complete, the training and feasibility assessment will be considered as complete and the subject will be considered as enrolled.

**Recording period:** During the recording period, the subject will be using the LENA recorder and will complete a daily questionnaire at the end of the each day. At the end of 7 days, the site will perform a phone call. The LENA cry and fuss clock generated from the LENA recorder data 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. If the primary caregiver consents for the use of Fitbit, the primary caregiver will be provided a Fitbit to record their vital parameters like heart rate and sleep through the 14 days after enrolment.
For the primary caregiver who consented for the use of Cocoon Cam will use the Cocoon Cam and would need to record the cry and sleep start and end time through the COOL app around the clock. In addition, the primary caregiver will need to complete a questionnaire on the usability of the Cocoon Cam.

**End of study:** At the end of the recording period , the primary caregiver will schedule an appointment with the PI. At the end of study visit, the primary caregiver will discuss the data provided by the LENA recorder and the COOL mobile app with the PI and PI will use the data to explain to the primary care giver if there is any specific crying pattern based on the objective data from LENA. The Primary caregiver and PI will complete a questionnaire each on the use of the data provided by the LENA recorder during their discussion.

For the primary caregiver who consented for the use of Cocoon Cam, the primary caregiver and HCP will need to complete a questionnaire on the usability of the Cocoon Cam.

## 6.2 Assessment windows

Attempts should be made to schedule visits (assessments) on the exact date. If this is not possible, visits (assessments) should be scheduled within the windows included below.
- Screening Visit (Day 0 to -2) / For Cocoon Cam cohort Screening Visit (Day 0 to -7)
- Enrolment Visit (Day 0)
- Phone call visit (Day 7 +2 days)
- End of study visit (Day 14 +7 days)

## 6.3 Assessments

### *6.3.1 Demographics*

Demographics include date of birth, sex, race and ethnicity.

### *6.3.2 Birth characteristics*

Birth characteristics include gestational period, gestational age and mode of delivery

### *6.3.3 Household Characteristics*

Order of the child in the household, number of siblings, subject's and sibling's child care

### *6.3.4 Relevant medical history (including pre-existing conditions)*

Relevant medical history is defined as any relevant medical event that occurred before enrolment in the study.

Any medical condition that the subject is born with, e.g. congenital abnormality / malformations will be recorded as pre-existing condition.

Relevant medical history and pre-existing conditions will be recorded on the Relevant Medical History and Pre-Existing Condition page in the CRF, including history of any disease and the occurrence of relevant medical events and relevant surgeries in the past.

### *6.3.5 Relevant concomitant medications*

The use of (relevant) medication due to medical history or any adverse event related to the study product must be recorded on the Concomitant Medications page in the CRF.
The Investigator must ensure that all required information is captured on this page, including:

- Name of Medication;
- Dose and unit;
- Frequency;
- Route of administration;
- Start and stop date;
- Indication: Adverse event.

### *6.3.6 Feeding characteristics*

The Feeding characterises will be collected through self-reported feeding questionnaire by the primary caregiver. The questionnaire will collect the food type including breastfeeding, infant or follow on formula, water, beverage and complementary food intake for the period of 1 week prior to the screening visit.

### *6.3.7 Primary Caregivers Characteristics*

Date of birth. Mobile usage, highest level of education, occupational status

### *6.3.8 Questionnaires*

Infant's crying pattern and caregiver experience of subject's crying and/or fussing for last 7 days before enrolment will be collected through primary caregiver reported questionnaires on the mobile app at enrolment.

The primary caregiver's feedback on the use and relevance of the data provided by the LENA recorder and their feedback on the level of engagement due to the content on the COOL mobile app will be collected through self-reported questionnaires at day 7 and 14.

A daily questionnaire on the average total minutes the subject cried/fussed and the time of the day the subject cried or fussed most based on primary caregiver's perception will be collected for 14 days from enrolment through primary caregiver reported questionnaires on the mobile app.

For the primary caregiver who consented for the use of Cocoon Cam, cry and sleep time for the infants around the clock will be collected using the COOL mobile app. The usability of the Cocoon Cam by the primary caregiver will be collected through questionnaire at day 7 and 14.

At the end of the study post clinic visit, a questionnaire to understand if the information from the LENA recorder helped to objectively articulate the primary caregiver's discussion with the PI will be collected through primary caregiver reported questionnaires on the mobile app.

At the end of the study post clinic visit, a questionnaire on feedback from the HCP on the usability and relevance of the cry and fuss data generated by the LENA recorder in their daily practice will be collected.
For the primary caregiver who consented for the use of Cocoon Cam, a feedback from the HCP on the usability of the Cocoon Cam will also be collected.

#### *6.3.9 Data from Fitbit*

Vital parameters like heartrate and sleep pattern from Fitbit of the primary caregiver.

#### *6.3.10 Data from Cocoon Cam*

Sleep, Crying data captured by Cocoon cam and the usage data for the Cocoon Cam app .

#### *6.3.11 Study compliance*

Compliance is categorized as:
- Adherence in answering to the daily questionnaire
- Use of the LENA recorder
- Adherence to the visit window

#### *6.3.12 End of study evaluation*

Participants may be asked for their feedback on study participation. This is voluntarily and the encoded data will not be linked to the participants. Danone Nutricia Research will use the data to improve future studies. The encoded data will not be reported as study outcome parameter.

# 7 PRODUCTS

## 7.1 Name and description of the product

LENA is a commercially available device that parents, pediatricians, speech language pathologists, and researchers use to obtain information about a child's language environment and language development. Its language statistics were validated in a large-scale study that established norms for words, turns, and vocalisations. The device is now modified to also record crying and fussing.

The LENA recorder model# 0121 used for this study is a lightweight, pocket-size, rechargeable electronic device. This recorder can be placed securely into the specially designed infant's clothing as provided by the Sponsor. The specially designed garments are washable and reusable. After 24-hour use and removal from the clothing, the recorder can be connected to the uploader, the data is uploaded to a cloud online platform and subsequently erased from the in-home recorder. The connection with the uploader also allows the recorder to be subsequently recharged. The infant's primary caregiver will be supplied with 2 identical recorders that will be used interchangeably (one recorder is recording while the other is recharging).

The COOL mobile app is a mobile application available to the primary caregiver during their period of enrollment in this study to answer questionnaires, view the cry and fuss clock generated from the LENA recorder data and to provide them insights on infant's crying and fussing.

For the cohort consenting for Fitbit and Cocoon cam, the primary caregiver will receive Fitbit and Cocoon camera as part of study product.

### 7.2 Summary of known and potential risks and precautions

There is no known risk from the LENA recorder , COOL mobile app, Fitbit and Cocoon Cam. The LENA Recorder has been tested extensively against U.S., European, and Australian standards. The Recorder meets or exceeds most of the device compliance standards [Appendix 2]. Cocoon camera as well meets or exceeds most of the device compliance standards [Appendix 5].

### 7.3 Product handling

#### *7.3.1 Storage and distribution*

The LENA recorders, Fitbit and cocoon camera are to be stored at the Site officeat room temperature, then distributed to the primary caregiver at the screening visit. An inventory of the study product is maintained to track the distribution and supplies of the LENA recorders, uploaders, specially designed garments (e.g. T-shirts), Fitbit and Cocoon Cam.

### 7.4 Shipping/Distribution to/from the subjects

During screening visit, primary caregiver of the subject will receive two LENA recorders, an uploader and four specially designed garments (e.g. Vest, T-shirt, onesies), Fitbit (in case the primary caregiver consent for the use of Fitbit in the study, Cocoon Cam (in case consented for Cocoon Cam) and a courier return shipping envelope. In case, the subject is screen failure after training period, the subject will return both the LENA recorders, uploader, Cocoon Cam, Fitbit and the un-used clothing. In case the subject is enrolled, at the end of the study visit the subject will return the LENA recorder and uploader at the end of the study. The primary caregiver may retain the clothing, Cocoon Cam and the Fitbit.

### 7.5 Product accountability and reconciliation

The Investigator agrees not to supply the study product(s) to any person except the families participating in this trial. Study product must not be traded or discarded. Used and unused study products should be returned to the Sponsor upon completion of the study and/or study exit.

## 8 RANDOMISATION

Not applicable

## 9 ASSESSMENT OF SAFETY

Safety will be assessed and reported per the ICH-GCP guidelines.

### 9.1 Specification of Safety Parameters

An **Adverse Event (AE)** is defined as any untoward occurrence in a subject or clinical investigation subject using the described devices (LENA recorder and/or uploader) and which **does not necessarily** have to have a causal relationship with the study product (LENA recorder and/or uploader).

The AE may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study product/Investigational Product (IP)
- A combination of two or more of these factors

Adverse events are illnesses, signs or symptoms (including an abnormal laboratory finding) occurring or worsening during the study. Adverse events can be serious or minor. They may or may not lead to the withdrawal of the subject from the study. All adverse events must be documented and assessed for intensity, seriousness and relationship to the study product.

All AEs occurring during the study that are related (Probably or Certainly) to the study product will be recorded in the case report form (eCRF). Investigators must know and record the following information about adverse events:

- Description of event
- Duration
- Frequency
- Intensity
- Seriousness
- Action taken
- Outcome and sequelae
- Relationship to study product
- SAE (Yes/No)

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported in the medical history.

### 9.2 Intensity

Intensity of AEs can be categorized as follows:

- Mild: Symptoms hardly perceived, only slight impairment of general well-being
- Moderate: Clearly noticeable symptom(s), but tolerable without immediate relief
- Severe: Overwhelming discomfort

### 9.3 Seriousness

The use of the term “adverse event” does not imply a relationship with the study product or with the study. Adverse events fall into the categories “non-serious” and “serious”.
A **serious adverse event** is any untoward medical occurrence which:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly or birth defect during pregnancy

Any other important medical event that may not result in death, be life threatening or require hospitalization, may be considered a serious AE when, based upon appropriate medical judgment by the principle investigator or the medical doctor in the study team, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
**Non-serious:** all other adverse events not corresponding to the definition of serious adverse event are considered as non-serious.

### 9.4 Relation to study product

The PI or their designee will assess the possibility of a causal relationship between the study product and an adverse event based on the following criteria:

- **Unrelated**: There is an evident other explanation for the AE, e.g.:
  - The AE is obviously explained by a patient's pre-existing disease;
  - The AE is in accordance with the effect or adverse effect of the concomitant medication;
  - The AE has already occurred prior to the use of the study product.

- **Unlikely relation:** Reasonable temporal relationship with the use of the study products, but there is another plausible explanation for the occurrence of the AE.

- **Probable relation:** Reasonable temporal relationship with the use of the study product and plausible reasons point to a causal relationship with the study product.

- **Certain relation:** Reasonable temporal relationship with the use of the study product and
  - There is no other explanation for the AE, and
  - Subsidence or disappearance of the AE on withdrawal of the study product use (de-challenge), and
  - Recurrence of the symptoms on re-challenge

### 9.5 Methods and Timeline of Safety Reporting

The period of observation for collection of AEs begins when the family receives the study products and continues throughout the duration of the study. If the Investigator detects a serious AE in a study subject after the end of the study and considers the event possibly related to prior study product, he or she should contact the study monitor or primary designated Contract Research Organisation (CRO) personnel to determine how the AE should be documented, followed-up and reported.

### 9.6 Procedures for Adverse Event Reporting and Documentation

#### *9.6.1 Monitoring and Reporting of AE/SAE*

Briefing instructions on adverse events monitoring and reporting will be included during the enrolment of the infant. Reporting of adverse event will be done by the primary caregiver to the Site Study staff by telephone. An appropriate telephone number will be made available to the primary caregiver for this purpose. If the PI is not also the physician in charge, the latter will be notified accordingly and will evaluate medically and assess to determine their intensity, seriousness and relationship of the adverse events. He/she will record the medical information in the AE/SAE forms including, but not limited to the subject, date, description of event, duration, frequency, intensity, seriousness, action taken, outcome and sequel, relationship to the study product.

#### *9.6.2 Follow up*

All AEs/ SAEs related to the study product must be followed up until the outcome is known. The Investigator will continue to follow all serious adverse events (SAEs) or other AEs that were regarded as being definitely, or possibly related to the study product until they resolve or stabilize. This follow-up by the Investigator, if required, may extend beyond the end of the study period. All follow-up examinations and/or laboratory findings must be documented and reported.
In the case of serious adverse event(s) persisting beyond trial termination, a follow-up visit with a physician may be required. Furthermore, if further analyses are required for the evaluation of a potential cause-effect relationship between the study product and the adverse event, all examinations and laboratory analysis and their results will be documented in the case report forms or in an attached file.

#### *9.6.3 Timeline of reporting*

**AE/SAE Procedure/Sponsor:** The Investigator must be notified of all adverse events related to the study product who will then notify the physician, if needed, who would conduct medical evaluation on intensity, seriousness and assign causality or relationship to study product.
**AE/SAE Procedure/Primary caregiver:** If the AE/SAE requires immediate medical treatment, the primary caregiver should take the child to their physician or local emergency room or urgent care centre for proper

medical care. The parent/guardian will contact the PI at their earliest opportunity so that proper documentation can be obtained and processed.
All SAE related to the study product must be reported to designated contract research organisation (CRO) by the Investigator within 24 hours of knowledge of the event. Designated contract research organisation (CRO) will notify the Sponsor (Danone) within 24 hours of learning the SAE.

#### *9.6.4 Reporting*

The Sponsor or designated CRO, on behalf of Sponsor, should expedite the reporting to all concerned institution(s), to the IRB(s)/EC(s), where required, and to the regulatory authority of all adverse events (AEs) that are both serious and related to study product.
Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.
The Sponsor or designated CRO. On behalf of the Sponsor, should promptly notify all concerned institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/EC's approval/favourable opinion to continue the trial.
All SAEs related to the study product will be reported to the ethics committee/IRB, PI and Sponsor.

### 9.7 New relevant safety information

The Sponsor will inform the Investigator and the reviewing accredited IRB/IEC if anything occurs that may negatively affect the burden or risks of participation as foreseen in the research proposal. The study may be suspended pending further review by the accredited IRB/IEC, provided that suspension does not jeopardise the subjects' health. The Investigator will take care that all subjects are kept informed.

## 10 STATISTICS

### 10.1 Sample size calculation

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.

### 10.2 Interim analysis (optional)

Not applicable

### 10.3 Subjects data sets

The analysis of the primary outcome parameter will be based on the All-Subjects-Enrolled (ASE) and Full-Analysis-Set . Definitions of the data sets will be described in detail in the Statistical Analysis Plan, which will be finalized before database lock for the study.

### 10.4 Descriptive statistics

Descriptive statistics will be provided for age and gender baseline characteristics as well as any pertinent demographics, household and feeding characteristics.

### 10.5 Statistical methods for data analysis

The method of analysis of the primary, secondary and exploratory outcome parameters will be detailed in the Statistical Analysis Plan.

# 11 ETHICAL CONSIDERATIONS

## 11.1 Basic principles and regulations

The Investigator must ensure that this study is conducted in full conformance with the principles of the 'World Medical Association Declaration of Helsinki' (64th WMA General Assembly, Fortaleza, Brazil, October 2013), International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (ICH-GCP (R2)), as appropriate for nutritional products and local legislation of the country in which the research is conducted, whichever affords the greater protection to the participants.

Danone Nutricia Research conducts all clinical studies in infants and young children in compliance with WHO guidelines by:

- Acknowledging the importance of the International Code of Marketing of Breast Milk Substitutes and subsequent relevant World Health Assembly resolutions
- Supporting the WHO's global public health recommendation for exclusive breastfeeding for 6 months and the introduction of safe and appropriate complementary foods thereafter
- Encouraging and supporting the UNICEF/WHO Baby Friendly Hospital Initiative (BFHI)

## 11.2 Roles and responsibilities

Roles and responsibilities of all parties involved in the study are in line with ICH-GCP. Roles and responsibilities of experts involved in protocol development and third parties have been listed in Appendix 3.

## 11.3 Institutional Review Board/Independent Ethics Committee

The Investigator must assure that this protocol and any accompanying material provided to the subjects, such as information and informed consent sheets, are submitted to the applicable IRB/IEC, according to local legislation. Approval from the IRB/IEC must be obtained before the start of the study, and must be documented in a letter specifying the date on which the IRB/IEC met and granted the approval, the composition of the IRB/IEC, and version and date of all submitted documents. The Investigator must assure that a status report is submitted at least annually to the IRB/IEC that approved the protocol. Danone Nutricia Research could assist in the preparation/submission process depending on local legislation.

Important protocol modifications (e.g. changes in eligibility criteria, outcomes, analyses) will be documented as substantial protocol amendment and will be provided to the applicable IRB/IEC for review according to legislation. Investigators must sign for agreement and subjects will be informed as appropriate. Relevant sections in the public trial register will be updated accordingly.

## 11.4 Recruitment and Informed Consent

Parents/Guardians of potentially eligible participants will be informed about the study and what is expected in case of participation to the study. Information on the study is incorporated in the Informed Consent Form. The parent/guardian must be given as much time as needed to read and understand the Informed Consent Form, to ask questions, and to reach a decision, including time for consultation with family members or others. Adequate time and resources must be provided for informed-consent procedures.
If the parent/guardian is willing that his/her child will participate, he/she will be asked to sign the Informed Consent Form. The Investigator or delegate carrying out the procedure will co-sign and date the Informed Consent Form. The parent/guardian has the right to make a request to withdraw his/her child from the study at any time, without giving any reason, without patient's medical care or legal rights being affected.

The main consent will include:

- Participation in the COOL study, agreement on all analyses of data as per protocol
- Use of personal information in encoded form within the scope of the research as defined in the Protocol (including e.g. future post-hoc analyses)
- Transfer of encoded personal data outside of the SG

If the parent/guardian of the subject does not agree with one of the above, he/she cannot participate in the study.

Additional consent will include:

- Use of personal information in encoded form for future research out of scope of study purposes, i.e. research related to broader scope of Early Life Nutrition
- Contacting the subject in the future for follow-up studies
- Consent for the use of Fitbit and analyse the data generated from Fitbit for primary caregiver
- Consent for the use of Cocoon Cam

If the parent/guardian of the subject does not agree with one of the above, he/she can participate in the study

In case, the primary caregiver of the infant is not the parent who signed informed consent, then a separate informed consent will be signed by the primary caregiver to consent to use the Fitbit during the study.

### 11.5 Confidentiality of study data

The Investigator is responsible for treating study information as confidential. The Investigator should ensure that the subject's identity is not made available to others than trained study staff and study coordinator. All subject study records will be encoded using a unique subject identifier, to maintain subjects' confidentiality. The unique subject identifier is generated from the country code, site number and the screening number.
The site number is generated by Danone Nutricia Research and will be communicated to each site. The screening number is assigned by the investigator when informed consent is obtained.
The Subject Identification Log that links subject codes/identifiers to the subjects' identity must be stored in the Investigator Site File and will not be sent to the Sponsor.
The Investigator is responsible for informing study participants on the review, collection, transfer, processing and archiving of (coded) personal data during the Informed Consent process.

A data leak can be defined as a loss or unauthorized processing of personal data, or the revelation of a lack of security that compromises the security, confidentiality or integrity of such information. In the event of a personal data leak, or any other circumstance in which Danone Nutricia Research is required to provide a notification under applicable law, the Investigator must inform Danone Nutricia Research without undue delay and will promptly investigate the data leak and take reasonable measures to identify its root cause(s) and prevent a recurrence. Danone Nutricia Research is as the data controller responsible to ensure that the subject(s) and/or the relevant representative(s) are informed.

### 11.6 Potential benefits and risks

There is no direct benefit and risk from the study for the primary caregiver and/or parent and/or guardian of the subject. The information obtained from this study will help to better understand the usability and relevance for primary caregiver and HCPs of a digital platform for infant crying and fussing.

### 11.7 Incidental findings procedure

An incidental finding is defined as "a finding that has potential health or reproductive importance which is discovered in the course of conducting research, but is beyond the aims of the study". The Investigator must inform subjects that if, in the course of research, incidental findings are discovered, they and/or their general practitioner will be informed of the finding in order to provide treatment made available by the local health-care system.

### 11.8 Incentives/Compensation for subjects

The subject's parent(s)/guardian(s) or their legally acceptable representative(s) will receive a compensation for the costs of transport to the investigational site and the fees for the clinic visits. If the primary caregiver provide consent to use the Fitbit, then the Fitbit can be retained by the primary caregiver.

### 11.9 Insurance

Danone Nutricia Research has arranged insurance covering any damage to subjects through injury or death caused by the study product and/or study procedures, and liability insurance, both according to local legislation.
Danone Nutricia Research will provide the Investigator with a copy of the insurance certificate(s), and updates if applicable.

## 12 ADMINISTRATIVE ASPECTS AND PUBLICATION

### 12.1 Study monitoring and audits

The study will only start at a site after:
- the IRB/IEC has granted approval for the conduct of the study
- essential documents are in place, such as Disclosure of Interests Form, Curriculum Vitae of the Investigator and site staff, and the Clinical Trial Agreement
- the study product has been released

Study monitoring under responsibility of Danone Nutricia Research by qualified staff will be performed at various stages of the study. Monitoring will include on-site visits to assure that the investigation is conducted according to the protocol and in order to comply with applicable regulations and deadlines. On-site review of Case Report Forms (CRFs) will include the review of forms for completeness, clarity, and consistency with source documents available for each subject.

The Investigator must permit study-related monitoring visits, audits, review by the IRB/IEC and regulatory inspections, and allow direct access to source data and source documents provided that subject confidentiality is protected. Danone Nutricia Research will plan study and site audits based on an annual audit schedule or on ad hoc basis (i.e. for cause audits). All audits will be performed by an independent auditor/agency. Investigators will receive written notice in advance in case Danone Nutricia Research decides to schedule a site audit at their site.

### 12.2 Source data

All information recorded in the CRF should be traceable in source documents, preferably in the subjects' (medical) records, or alternatively in other sources (e.g. source document worksheets, which may be provided by Danone Nutricia Research to capture study specific details that are not routinely recorded in the medical records), as documented per the Source Data Agreement Form. The data collected through the COOL mobile app and LENA recorder will be considered as source data.

### 12.3 Data handling

A 21 CFR Part 11 compliant mobile application and web application will be used to collect data for this study. The LENA audio data will be uploaded directly to the LENA server located in United States for processing through the uploader via secure internet connection. These documents will be finalised prior to the go-live of the mobile and web application. The recorded data from Fitbit and Cocoon Cam will be transferred to the AWS cloud servers located in United States where it will be stored and processed. All system used to store recorded data will have restricted physical access, network firewall security, VPN-based access and with antivirus and anti-malware software installed on the system. Access control and regular data backups will ensure that the data is protected against damage. The detailed process , data flow and data transfer guideline will be defined in Data Management Plan.

### 12.4 Documentation and storage

Danone Nutricia Research will provide the Investigator with an Investigator Site File (ISF). The Investigator is responsible for keeping this ISF updated and available for review by the study monitor.

Study documents must not be destroyed without prior written agreement between Danone Nutricia Research and the Investigator. All documents pertaining to the conduct of the study must be kept by the Investigator for a period of 15 years. Should the Investigator wish to assign study documents to another party, or move them to another location, Danone Nutricia Research must be notified first.

### 12.5 Temporary halt and premature termination of the study

Both Danone Nutricia Research and the Investigator reserve the right to discontinue the study at any time as defined in the Clinical Trial Agreement. Should this be necessary, the procedures for premature termination of the study will be arranged after review and consultation by both parties. When terminating the study, Danone Nutricia Research and the Investigator will assure that adequate consideration is given to the protection of the interests of all subjects. The sponsor will notify the accredited IRB/ IEC and relevant Health Authorities, according to local legislation, of the end of the study within a period of 90 days or earlier if required by local legislation. The end of the study is defined as the last subject's last visit.

### 12.6 Investigators' access to study data

Danone Nutricia Research is the exclusive owner of the study data as mutually agreed on in the Clinical Trial Agreement.
Proposals from Investigators for access to study data for research purposes will be evaluated by Danone Nutricia Research on following criteria: scientific quality and feasibility, relation/relevance to interests of focus of Danone Nutricia Research, and compliance with GCP and Good Laboratory Practice, where relevant.

### 12.7 Publication policy

Danone Nutricia Research takes responsibility for the registration of the study in a public clinical trial register. The intended trial register is www.clinicaltrials.gov.

In compliance with the declaration of Helsinki, Danone Nutricia Research strives to make the results of all clinical studies publicly available, regardless of whether the results reflect favourably or unfavourably on a product or whether the study was terminated early.
Results are disseminated by means of, amongst others, publication in peer reviewed journals, and/or by registering a summary of the clinical study results on a public trial register. Danone Nutricia Research strives to make a summary of study results available within 12 months after study completion.
Danone Nutricia Research and Investigator(s) will mutually agree on the publication policy in the Clinical Trial Agreement.

### 12.8 Sources of funding and other support

Danone Nutricia Research is responsible for funding the study. Financial arrangements between Danone Nutricia Research and the Investigator will be documented in a Clinical Trial Agreement.

## 13 RECORD OF REVISIONS

| Version | Nature of Revision |
|---|---|
| 1.0 | Document creation |
| 2.0 | Document revision |
| | |

## 14 REFERENCES

1. Barr RG (1990) The normal crying curve: what do we really know? Dev Med Child Neurol 32
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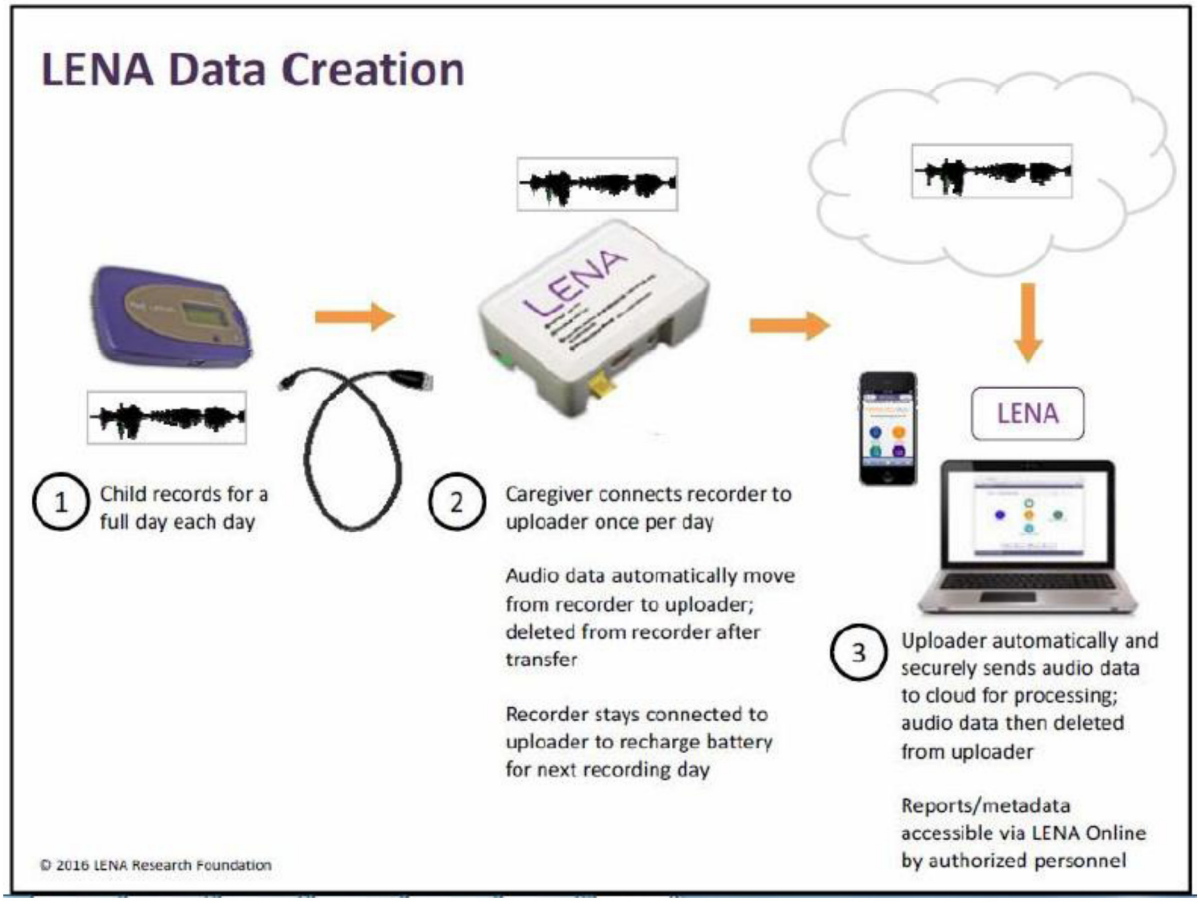
## APPENDIX I LENA DATA FLOW



## APPENDIX II LENA RECORDER COMPLIANCE

LENA RESEARCH FOUNDATION

*Nurturing minds, changing lives*

### LENA Recorder Compliance Standards

The LENA Recorder has been tested extensively against U.S., European, and Australian standards. The Recorder meets or exceeds the following compliance standards:

| Compliance Standard | LENA Recorder Model #0121 | LENA Recorder Model #0122 |
|---|---|---|
| Standards for audio, video, and similar electronic apparatus | UL 60065 & IEC/EN 60065 | |
| Canada standards for audio, video, and similar electronic apparatus | CAN/CSA-C22.2 No. 60065 | |
| Standards for electric toy safety | UL 696 | ASTM F963-11 |
| European Union standard for information technology radio disturbance characteristics | EN 55022 | |
| FCC radio interference standards for digital devices | FC | |
| European standards for health, safety, and environmental protection | CE | |
| Australian standards for information technology equipment | | |
| Standards for restriction of hazardous substances | RoHS | |

### Declaration of Conformity

Manufacturer: LENA Research Foundation
5525 Central Ave, Suite 100
Boulder, Colorado 80301
USA

Product: LENA Recorder
Models #0121 and #0122

The undersigned hereby declares, on behalf of the LENA Research Foundation, that the LENA Recorder, to which this declaration relates, is in conformity with the provisions as outlined above. The technical construction file is maintained at the main office of LENA Research Foundation.

Stephen M Hannon, PhD
President

## APPENDIX III ROLES AND RESPONSIBILITIES

### RESPONSIBLITIES SOURCED OUT OR SHARED WITH THIRD PARTIES

The sponsor has appointed dedicated staff for protocol development, management of the study, data management, statistical analysis and interpretation of data, and writing of the report.
A full list of contributors is maintained throughout the study by the sponsor.

| Name third party | Location | Responsibility |
|---|---|---|
| TechObserver | Singapore | Contracted for project management , data management, statistical analysis, interpretation of data and writing headline result.<br>They are also been outsourced to develop the mobile and web application and provide study staff at the site. |

## APPENDIX IV SCHEDULE OF ASSESSMENTS

| n=20 | Screening | | Enrolment | Phone Call | End of study |
|---|---|---|---|---|---|
| | At Site | Training Period | Day 0 | Day 7 | Day 14 |
| Date of visit | X | | X | X | X |
| Informed consent | x | | | | |
| Demographic data | x | | | | |
| Birth characteristics | x | | | | |
| Medical history | x | | | | |
| Prior medication related to Medical History | x | | | | |
| Feeding characteristics | x | | | | |
| Household characteristics | x | | | | |
| Primary caregiver characteristics | x | | | | |
| Crying pattern history and primary caregiver experience | | | x | | |
| Daily Questionnaire | | | x | | |
| Day 7 and 14 primary caregiver questionnaire | | | | x | x |
| HCP Feedback Questionnaire | | | | | x |
| End of Study Questionnaire | | | | | x |
| Adverse event due to the study product | | x | | | |
| Concomitant Medication related to Adverse event due to study product | | x | | | |
| LENA recorder data | | x | | | |
| Fitbit | | | x (if consented) | | |
| Cocoon Cam | | | x (if consented) | | |

## APPENDIX V SAFETY CERTIFICATE FOR COCOON CAM

TCB

GRANT OF EQUIPMENT AUTHORIZATION

Certification
Issued Under the Authority of the
Federal Communications Commission
By:

TCB

PHOENIX TESTLAB GmbH
Koenigswinkel 10
32825 Blomberg,
Germany

Date of Grant: 10/01/2015

Application Dated: 10/01/2015

Shenzhen Smart-eye Digital Electronics Co.,Ltd
#6 Northern Zone, Shangxue S&T City, Bantian,
Longgang District,Shenzhen,China
Shenzhen,
China

Attention: Bella Zheng , Engineer

NOT TRANSFERABLE

EQUIPMENT AUTHORIZATION is hereby issued to the named GRANTEE, and is VALID ONLY for the equipment identified hereon for use under the Commission's Rules and Regulations listed below.

FCC IDENTIFIER: ZCB620GB
Name of Grantee: Shenzhen Smart-eye Digital Electronics Co.,Ltd
Equipment Class: Digital Transmission System
Notes: IP Camera

| Grant Notes | FCC Rule Parts | Frequency Range (MHZ) | Output Watts | Frequency Tolerance | Emission Designator |
|---|---|---|---|---|---|
| | 15C | 2412.0 - 2462.0 | 0.0031 | | |

Output power listed is peak conducted. This device has 20 and 40MHz BW modes.