ObvioHealth
The Digital Revolution Gets Clinical

STUDY PROTOCOL

Study Number	**OBVIO-DAN-002**
Title	**Observational Study: Image Collection of Infant/Toddler Stools for Danone Software Development**
Sponsor	**Danone**
Country	**United States**
Date	**12OCT2018**
Version Number	**2**

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PRINCIPAL INVESTIGATOR (PI) AND CO-INVESTIGATOR (CO-PI)

Parth Shah, MD

Sr. Director, Medicine and Economics

ObvioHealth

Jun 20, 2019

Date

PShah

PShah (Jun 20, 2019)

Signature

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the conduct of the study.

I will only use the informed consent approved by the sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB) responsible for this study.

I agree that the sponsor or its representatives shall have access to any source documents from which case report form information may have been generated.

2 Team Signature Page

CLINICAL PROJECT MANAGER

Jill Wong
Digital Program Manager
Digital Team, Early Life Nutrition
Danone Nutricia

Jun 20, 2019
Date

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PRINCIPAL SCIENTIST

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Date

Dr. Thomas Ludwig (Jun 20, 2019)

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Date

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OBVIOHEALTH PROGRAM LEADER

Cherlynn Basignani BSN, RN, CCRC

Senior Director, Clinical Operations

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Cherlynn Basignani BSN, RN, CCRC
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Signature

3 Abbreviations

BITSS	Brussels Infant and Toddler Stool Scale
CDM	Clinical Data Manager
CPM	Clinical Project Manager
CRO	Contract Research Organization
DHC	Data Handling Conventions
eCRF	Electronic Case Report Form
eIC	Electronic Informed Consent
GCP	Good Clinical Practice
HCP	Healthcare Providers
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Investigational Product
PI	Principal Investigator
SOP	Standard Operating Procedure
TMF	Trial Master File

4 Synopsis

Study Title	Observational Study: Image Collection of Infant/Toddler Stools for Danone Software Development
Study Objectives	***Primary*** • To create a database of stool images scored by mothers that are suitable for Danone software development purposes • To create a database containing at least 200 pictures of diapers containing fecal (stool) material per each stool consistency score (type 1 to 7) of the BITSS (Brussels Infant and Toddler Stool Scale) and 200 images of empty (no stool) disposable diapers ***Exploratory*** • To compare the stool consistency scores from mothers on-study to re-scores of mothers (not enrolled on-study) based only on the uploaded images • To assess mothers' perceptions of the usability of the stool scoring process and the usability of the ClaimIt app
Study Design	An observational study of stool images among infants/toddlers, ages 0-24 months
Study Observation Duration	30 days per child **NOTE:** If participants upload a low number of quality images due to infant/toddler constipation and infrequency of stooling, the mother may be asked if she would like to continue in the study for an additional >30 days or more. If she chooses to continue, she may do so as long as images continue to be provided at a reasonable frequency and/or until stool strata are satisfied (at the PI's discretion).
Country of Implementation	United States of America
Study Population	Approximately 100 healthy infants/toddlers (until 200 images per stool score reached), age 0-24 months (at time of enrollment)

Inclusion Criteria	• Healthy infants/toddlers (0-24 months of age at time of enrollment) • Informed consent from mother ≥18 years of age • In-home access to reliable internet connections; a mobile device suitable for electronic communication; and a device suitable for capturing and transmitting high-quality electronic images as per the PI's discretion • Infant/toddler consumes standard, age-appropriate food (breast milk; formula; commercial/homemade baby, table or finger food) • Based on the number of stools already acquired per relevant strata at time of enrollment, infant/toddler may or may not be required to regularly produce stools scored as a Score 1, 2, 6 or 7 (per Appendix II)
Exclusion Criteria	***Mothers of Infants/Toddlers:*** • The use of cloth diapers (mothers must commit to using disposable diapers for the duration of the study) • Known to have a significant condition (including during pregnancy) that might interfere with the study compliance, as per PI's clinical judgment • Deemed likely to be non-compliant with the study protocol, as per PI's clinical judgment

Endpoints	***Primary:***
	• Creation of a database containing at least 1600 pictures of individual diapers:
	  ○ 200 images of diapers with stool per each score (BITSS types 1 to 7)
	  ○ 200 images of empty (no stool) disposable diapers
	
	Exploratory:
	• A comparison of the stool consistency scores from the mothers on-study to re-scores from mothers (not enrolled on-study) based only on the uploaded images
	• An assessment of mothers' perceptions of the usability of the stool scoring process
	• An assessment of mothers' perceptions of the usability of the ClaimIt app

Study Implementation	***Prescreening***: Administer the inclusion/exclusion criteria eQuestionnaire to mother which includes infant/toddler's estimated stool frequency and consistency (e.g., liquid, soft/mushy, solid, firm, hard). After mother and infant/toddler's information is shown to satisfy predetermined prescreen criteria (including distribution by groups), the mother will be provided access to the ClaimIt app along with the following information: • How to complete the electronic informed consent (eIC), screening and enrollment process • Overview of trial tasks and relevant notifications • ClaimIt navigation: How to interact with the ClaimIt app during the observation period • Additional study details & instructions on how to take high-quality, standardized pictures with proper lighting • All relevant contact information that may be required during the study ***Screening:*** The mother will complete a detailed eQuestionnaire for confirmation of inclusion and exclusion criteria. The mother will also be asked to upload three (3) test images of their infant/toddler's stool via ClaimIt, each with a corresponding score based on her judgment made in comparison with the BITSS scoring tool. Images must be uploaded within 10 days of receiving ClaimIt app access. An adaptive recruitment approach will be leveraged to ensure that ≥200 pictures of each stool type are collected over the duration of the study. The mother and infant/toddler will be enrolled into the study if the test images are successfully uploaded, and they meet all the inclusion criteria and none of the exclusion criteria for the study, based on the PI's judgment and appropriate fit into predetermined bowel function strata. ***Observation Period:*** The mother will be asked to interact with the ClaimIt app daily for 30 days (or longer) as follows: • Two empty (no stool) disposable diaper images are to be uploaded: one at Baseline and one at End of Study ○ Images should be taken of the type of disposable diaper used most frequently for the infant/toddler

	○ Additional empty (no stool) disposable diaper images may only be submitted if the brand/type of diaper changes; if the diaper size changes, no additional pictures need to be uploaded • Stool images will be taken with a smartphone (or alternative suitable for capturing and transmitting high-quality electronic images) and uploaded daily: ○ Mothers will be given instructions on how to take high-quality, standardized pictures with proper lighting ○ Every bowel movement is to be imaged, potentially providing several images per day ○ Mothers who have not submitted at least one image in the previous 24-hour period will be sent notifications to encourage compliance ○ Only 1 representative image per bowel movement is to be transmitted • Along with each stool image uploaded, the mother will rate the stool characteristic type on the BITSS (type 1 to 7); scores will be based only on consistency and not color ***End of Observation Period:*** • The mother will be asked to complete an eQuestionnaire to assess and comment on the usability of the ClaimIt app and the scoring process (Appendix V) • Two mothers who were not enrolled in the study will be provided a collection of study stool images and asked to re-score each image according to the BITSS
Statistical Considerations	A sample size of 100 subjects is estimated with the following considerations: • Progression of potential subjects will be gated at the prescreening and screening steps to facilitate enrollment of an appropriately diversified set of infants/toddlers based on bowel patterns to reach 200 images per each stool consistency score (type 1 to 7) of the BITSS • The Sponsor and ObvioHealth will review the distribution of the scores and image quality and will determine when the prescreening requirements can be modified • A comparison will be made between the stool consistency scores from the mothers on-study to re-scores from mothers (not enrolled on-study) based only on the uploaded images

	• Based on Sponsor review of the data, the following may be performed:
	  ○ A post hoc analysis
	  ○ Descriptive summary statistics for categorical and quantitative data
	• The expectation is that not all the mothers will be compliant with study tasks for all 30 days
	• A dropout rate of 15% is anticipated (if dropout rate exceeds 15%, replacements will be made for all additional withdrawals)

5 Introduction

Accurately classifying stool consistency for infants and toddlers who are not yet toilet trained remains challenging. A recent study showed that among parents of infants and toddlers, only fair agreement existed between the parental report of stool consistency and the Bristol Stool Form Scale (BSS),[1] a gold standard in the classification of stool consistency in adults and older children who are toilet trained.[2] While there are alternative assessment methods which are used in clinical practice, such as the modified BSS and the Amsterdam Infant Stool Scale, a universally-accepted tool does not exist.[3] The Brussels Infant and Toddler Stool Scale (BITSS) was recently initiated based on the BSS to provide a classification tool to describe stool consistency for infants and toddlers.[4]

This observational study is designed to collect a series of images that span the range of stool consistencies associated with the stools of infants and toddlers to create a significant and varied photographic image database. For essentially healthy infants/toddlers (0-24 months) stool consistencies range from liquid (frequently associated with diarrhea) to hard formed (frequently associated with constipation) stools. This database will be used to assist in the further development of Danone software to facilitate evaluation of stool type remotely and permit evaluation beyond the interpretation of parents. The study is designed to collect at least 1600 images: at least 200 images per stool score (type 1 to 7) of the BITSS (at least 1400 total) plus 200 images of empty (no stool) diapers, generating further data to assist in the assessment and classification of infant/toddler stools and gastrointestinal function.

6 Objectives of the Trial

6.1 Primary Objectives

- To create a database of stool images scored by mothers that are suitable for Danone software development purposes
- To create a database containing at least 200 pictures of disposable diapers containing fecal (stool) material per each stool consistency score (type 1 to 7) of the BITSS (Brussels Infant and Toddler Stool Scale), and 200 images of empty (no stool) disposable diapers

6.2 Exploratory Objectives

- To compare the stool consistency scores from mothers on-study to the re-scores of mothers (not enrolled on-study) based only on the uploaded images
- To assess mothers' perceptions of the usability of the stool scoring process and the usability of the ClaimIt app

7 Trial Design

7.1 Study Calendar

	Pre-screening	Baseline	Daily	Weekly	End of Study
Prescreening Eligibility Review	X				
Prescreening Image Upload	X				
eIC	X				
Screening eQuestionnaire		X			
Upload of Stool Image(s)			X		
Sponsor and CRO Review of Images and Distribution of Scores				X	
End of Study eQuestionnaire					X

7.2 Type of Trial

An observational study of 100 essentially healthy infants/toddlers, 0-24 months of age.

7.3 Endpoints

Primary Endpoint:

Creation of a database containing at least 1600 images:

- At least 200 images of disposable diapers containing stool per each score (type 1 to 7) of the BITSS
- At least 200 images of empty (no stool) disposable diapers

Exploratory Endpoints:

- A comparison of the stool consistency scores from the mothers on-study to re-scores from mothers (not enrolled on-study) based only on the uploaded images
- An assessment of mothers' perceptions of the usability of the stool scoring process
- An assessment of mothers' perceptions of the usability of the ClaimIt app

7.4 Participants and Location

7.4.1 Participants

Study participants will include the mother and their infant/toddler. The prescreening recruitment process will be administered through an online eQuestionnaire to the mother evaluating the typical stool and consistency (e.g., liquid, soft/mushy, solid, hard).

7.4.2 Location

The trial will be conducted remotely in the United States. Communication between mothers and study personnel will be conducted via the internet (ClaimIt platform) and/or over the telephone or email messaging as appropriate.

7.5 Study Duration

It is expected that the enrollment period will be five (5) months in total.

The expected study duration is 30 days per mother and infant/toddler. If a participant uploads a low number of quality images due to infant/toddler constipation and infrequency of stooling, a member of the study team may contact the mother to ask if she wants to continue with study for an additional 30 days or more. If she chooses to continue, they may do so as long as images continue to be provided at a reasonable frequency and/or until stool strata are satisfied (at the PI's discretion).

8 Study Population

It is expected that the infant and their mother will sustain these eligibility criteria for the duration of their enrollment.

8.1 Subject Inclusion Criteria

Subjects must meet the following:

- Healthy infants/toddlers (0-24 months of age at time of enrollment)
- Informed consent from mother ≥18 years of age
- In-home access to reliable internet connections; a smartphone (or alternative suitable for capturing and transmitting high-quality electronic images) as per the PI's discretion
- The infant/toddler consumes age-appropriate, standard food (breastmilk; formula; commercial/homemade baby, table or finger food)
- Based on the number of stool images already acquired per relevant strata at time of enrollment, the infant/toddler may or may not be required to regularly produce stools scored as a Score 1, 2, 6 or 7 (per Appendix II)

8.2 Subject Exclusion Criteria

Mothers of Infants/Toddlers:

- The use of cloth diapers (mothers must commit to using disposable diapers for the duration of the study)
- Known to have a significant condition (including during pregnancy) that might interfere with the study compliance, as per PI's clinical judgment
- Deemed likely to be non-compliant with the study protocol, as per PI's clinical judgment

8.3 Subject Withdrawal Criteria

Mothers and their infants/toddlers may be withdrawn from the study at any time and for any reasons including but not limited to the following:

1) At their request or the request of their legally authorized representative.
2) If, in the PI's opinion, continuation in the study would be detrimental to the subject's well-being.
3) Poor compliance: if the mother and infant/toddler consistently do not adhere to the study procedures (per the PI's discretion).
4) Protocol deviation(s) which in the opinion of Sponsor warrant discontinuation from the study; e.g., violation of inclusion and/or exclusion criteria.

Study Note: If the infant/toddler experiences an illness (other than diarrhea/constipation) lasting longer than 7 days, has surgery or is admitted to the hospital for more than 24 hours, they should be withdrawn from the study immediately.

Due to the 15% dropout rate built into the estimated total sample size, subjects whose study participation is terminated prematurely for any of the above-listed criteria will not be replaced. If the dropout rate exceeds 15%, replacements will be made for all additional withdrawals. The PI will make every effort to contact subjects lost to follow-up during the study. Attempts to contact the subject will be documented in the subject's records (e.g., dates and times of attempted telephone contact).

The number and percentage of subjects who withdraw early and their reasons for withdrawal will be presented in a table and a CONSORT flow diagram equivalent.

The following information will be documented in the mother and infant/toddler's record in the event of a subject's withdrawal from the study:

I. Date of withdrawal
II. Reasons for withdrawal

Even if consent is withdrawn, all data and all images that were acquired before consent was withdrawn will be maintained.

9 Assessment of Safety

As this is an observational study and the study procedures present no more than minimal risk, adverse events are not expected and therefore not collected or reported for this study.

10 Execution of the Trial

10.1 Screening and Enrollment

Prescreening:

The prescreening recruitment step will recruit healthy infants/toddlers (0-24 months of age at enrollment) residing in the United States through an online eQuestionnaire administered to the mother. Questions will include an estimation of the frequency of stools of varied consistency (e.g., liquid, soft/mushy, solid, firm, hard). After satisfying predetermined prescreen criteria (including distribution by groups), the mother will be provided access to the ClaimIt app along with the following information:

- Overview of trial tasks and relevant notifications
- Instruction on how to complete the electronic informed consent (eIC), screening and enrollment process
- Instruction on how to interact with the ClaimIt app during the observation period
- Additional study details & instructions

The mother will be sent an electronic consent (eIC) for review and will have the opportunity to ask questions and receive answers either through online communication or in-person telephone conversation. Mothers who choose to participate will voluntarily sign an eIC as instructed by the ClaimIt app.

Screening and Enrollment

After the eIC is voluntarily signed, a detailed eQuestionnaire for confirmation of inclusion and exclusion criteria will be administered to the mother. She will also be asked to upload three (3) test images of their infant/toddler's stool via ClaimIt, each with a corresponding score, within 10 days of receiving ClaimIt app access. The mother and infant/toddler will be enrolled into the study if the mother successfully uploads the test images and scores and meets all the inclusion and none of the exclusion criteria for the study based on PI's judgment. Depending on the distribution of stool images already acquired per score, the mothers and infant/toddlers may be further qualified based on the likelihood of filling gaps in the image collection.

This adaptive recruitment approach will be leveraged to ensure that ≥200 pictures of each type are collected over the duration of the study. The enrollment of potential subjects will be gated at either (or both) the prescreening and screening steps based on the infant/toddler's most common stool consistency (e.g., liquid or hard stool).

The sponsor (Danone) and the CRO (ObvioHealth) will review images and the mothers' BITSS scores to assess the overall distribution of images per each score and will determine when the prescreening requirements can be modified. Total study enrollment may be expanded or modified until target values are attained.

10.2 Data Collection

The mother will be asked to interact with the ClaimIt app daily for 30 days (or more) as follows:

- Stool images will be taken with a smartphone (or alternative suitable for capturing and transmitting high-quality, electronic images) and uploaded daily
- Every bowel movement will be photographed, potentially providing several images per day
    - Only 1 representative image per bowel movement should be transmitted
- If the mother has not uploaded an image in 24 hours, a notification and the Compliance eQuestionnaire requiring a response will be sent to her (Appendix IV)
- The following steps should be taken to ensure the image quality:
    - The picture should be taken in a well-lit room and with sufficient lighting on the diaper itself; pictures should not be taken in rooms requiring flash
    - The diaper should be placed on a table or area apart from any other objects; primarily only the soiled portion of the diaper should be in the picture
    - The diaper must be fully opened, and the contents must be clearly visible in the photograph

- The camera should be zoomed-in as appropriate and focused on the stool itself
    - The image will include all the stool while excluding as much of the dry diaper as is reasonable
- The pictures should be taken within 10 minutes after the child has soiled the diaper
    - Images in which the stool form is not recognizable (e.g., stools that have been distorted or significantly smushed) should not be uploaded

- Along with each stool image uploaded, mothers will rate the stool consistency type compared to examples provided by the BITSS (Score 1 to 7)
    - Scoring will be based only on consistency, not color
    - Sample images of each score will be provided
- A total of two empty (no stool) disposable diapers, spread open, are to be submitted: one at Baseline and one at the End of Study
    - Images should be taken of the type of diaper used most frequently for the infant/toddler
    - Additional empty (no stool) disposable diaper images may only be submitted if the brand/type of diaper is changed; if only the diaper size changes, no additional pictures need to be uploaded

10.3 End of Study

At the end of the study, the mother will be asked to complete an eQuestionnaire to assess and comment on the usability of the ClaimIt app and the scoring process (Appendix V).

Also, the Sponsor will identify two mothers who were not enrolled in the study. They will be provided a collection of uploaded study images and asked to re-score each image according to the BITSS.

10.4 Application Description

The ClaimIt app is a mobile application available to study participants during their period of enrollment so they can perform certain study-related tasks and receive and transmit communications from and to the CRO staff.

10.5 Monitoring

The study will be monitored on an ongoing basis beginning with enrollment of the first mother and infant/toddler and continuing through the study exit of the last enrolled pair. Regular monitoring will be done by the designated ObvioHealth personnel during the study. The monitoring activities will be detailed in a monitoring plan. The following measures are in place to ensure consistent and regular engagement by the mother:

- Dedicated study personnel will maintain contact with the mother to answer questions about the study or the ClaimIt app, as necessary
- In some circumstances, the PI or study team personnel may call the mother to determine the compliance with study protocol
- Study team (Sponsor and CRO members) will review the BITSS scores provided by the mothers to assess the distribution of strata and daily compliance which includes:
    - Adherence to study protocol; including sustained quality of images
    - Proper uploading of the images in a timely manner
- If the mother has not uploaded an image in the previous >24 hours, a notification and the Compliance eQuestionnaire will be sent (Appendix IV)

Since there are no physical sites involved in this protocol, monitoring will be implemented throughout the study via remote data reviews. The monitor will check

eCRF data for completeness and consistency. Protocol deviations will be reported in the monitoring report and a corrective action plan implemented, as necessary. The monitor will communicate any detected protocol deviations to the PI. These deviations will be recorded in a Protocol Deviation Log.

Electronic CRFs (eCRFs) will be completed by the mother for their infant/toddler. Data from the completed eCRF will then be reviewed by the designated study team member and if any errors are identified, they may be corrected consistent with the Data Handling Conventions (DHC) or may be addressed through direct contact with the mother.

10.6 Computerized Data Entry - Security and Privacy of User Data

All data is hosted on Microsoft Azure service. All ObvioHealth employees and their affiliates are bound by strict confidentiality agreements. Transport Layer Security (TLS) is used to secure all data in transit.

10.7 Computerized Edit Checks

The database will incorporate the needed programmed edit checks to help ensure quality data. Messages to the mother may be generated automatically to alert her to any entry error.

10.8 Audit Trail

All entries and alterations made in the database will be captured by an audit trail in which the individuals accessing the database and providing entries and/or making alterations are identified via their user IDs and passwords.

11 Statistics

11.1 Sample Size Calculations

A sample size of 100 subjects is estimated to be sufficient to collect images of at least 200 pictures of diapers containing fecal (stool) material per score (type 1 to 7) of the BITSS plus 200 images of empty (no stool) disposable diapers.

12 Legal and Ethical Prerequisites

12.1 Legal Requirements

The study will initiate after approval from the IntegReview IRB which follows the guidance of USA regulatory bodies and general Good Clinical Practice (GCP)/International Conference on Harmonisation (ICH) regulations.

12.2 Ethical Aspects

12.2.1 Protection of the Subject's Confidentiality

Confidentiality of all study participants will be maintained; codes for subject identification will be utilized. Subjects will review and complete the HIPAA release of information form during the eIC process.

12.2.2 Informed Consent

Electronic Informed Consent (eIC) signed by the subject indicating their consent to her and her infant/toddler's participation in the study is required. This will be completed prior to conducting any study-related activities and will be done in accordance with all applicable regulatory requirements.

The eIC will inform the mother about all aspects of study participation. Dedicated study personnel will be available to the parent to answer questions about the study or the informed consent. The IRB/EC will approve the eIC. Any amendments to these documents must be approved by the IRB/EC.

The mother must sign the eIC prior to the initiation of any study-related activities beyond prescreening.

The decision to participate in the study is entirely voluntary. The PI and/or his/her designee must emphasize to the mother that the consent to participate can be withdrawn at any time without penalty or loss of benefits to which the mother and infant/toddler are otherwise entitled.

12.2.3 Ethics Committee Approval

The study protocol will be submitted by the PI (or designee) for examination by the US Institutional Review Board (IRB)/EC. Commencement of the clinical trial is not permitted without written approval of the IRB/EC.

The IRB/EC must be notified of all subsequent additions or changes in the study protocol. If a protocol amendment is made and approved by the IRB/EC, subjects must re-sign the ICF after review to remain in the trial.

12.2.4 Declaration of Helsinki

This trial will be conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments.

13 Quality Control and Quality Assurance

13.1 Monitoring

Since there are no physical sites involved in this protocol, monitoring will be implemented throughout the study via remote data reviews. The monitor will check eCRF data for completeness and consistency.

The main protocol deviations for consideration on this trial are:

- Informed consent process not adequately performed
- Violation of inclusion and/or exclusion criteria
- Non-compliance with study-related daily requirements
- Any other GCP non-compliance

Protocol deviations will be tracked and logged in the Protocol Deviation Log.

At the end of the trial, the Monitor and/or Clinical Data Manager (CDM) will ensure that all documentation and the trial master file (TMF) are complete. In all cases, it is the responsibility of the CPM, CDM and study team to maintain subject confidentiality.

13.2 Quality Control

13.2.1 Quality Control of Essential Documents

ObvioHealth will implement and maintain quality assurance, and quality control systems with Standard Operating Procedures (SOPs) to ensure that this clinical trial is conducted, and data are generated, documented (recorded) and reported in compliance to the protocol, GCP/ICH standards, and other applicable local regulations.

13.3 Responsibilities of the PI

The PI is responsible for the following:

- Selection of participants/subjects in accordance with the inclusion and exclusion criteria (in this study the mother and infant/toddler)

- Maintain confidentiality and safety of subjects in accordance with the Declaration of Helsinki
- Adherence to the study protocol and the spirit of GCP
- If modification becomes necessary, the rationale will be provided in a protocol amendment signed by the PI and Sponsor for submission to the IRB/EC
    - After the protocol amendment approval, subjects may be required to re-sign the eIC to remain in the trial
- During the trial, provide subjects with any newly available information that may be relevant to them
- Cooperation in the case of an audit and/or a regulatory inspection, providing direct access to data and/or documents

14 Study End Procedures

14.1 Premature Termination of Study

Should it prove necessary to discontinue the study permanently prior to completion, the Sponsor will notify ObvioHealth, the subjects, and the IRB/EC of the rationale. All relevant study documents and data will then be sent to the Sponsor.

14.2 Termination of Study

After the completion or termination of the study, all relevant study documents and data will then be sent to the Sponsor. The PI will inform the IRB/EC of the end of the study, and a certificate of study closure will be issued.

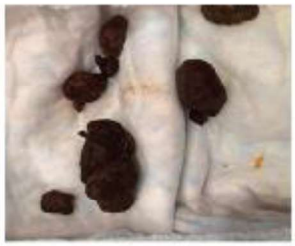
15 References

1. Koppen IJ, Velasco-Benitez CA, Benninga MA, et al. Using the Bristol Stool Scale and parental report of stool consistency as part of the Rome III Criteria for functional constipation in infants and toddlers. J Pediatr 2016;177:44–8.e1.
2. Heaton KW, Radvan J, Cripps H, et al. Defecation frequency and timing, and stool form in the general population: a prospective study. Gut 1992;33:818–24
3. Lane, M.M., Czyzewski, D.I., Chumpitazi, B.P., and Shulman, R.J. Reliability and validity of a modified Bristol Stool Form Scale for children. J Pediatr. 2011; 159: 437–441.
4. Vandenplas Y, Szajewska H, Benninga M, et al. Development of the Brussels Infant and Toddler Stool Scale ('BITSS'): protocol of the study. BMJ Open 2017;7:e014620.

16 Appendices

APPENDIX I: Brussels Infant and Toddler Stool Scale (BITSS)

Refer to the following BITSS (Score 1 to Score 7) images in order to rate each stool image prior to uploading through the ClaimIt app:



SCORE 1

SCORE 2

SCORE 3

SCORE 4

SCORE 5

SCORE 6

SCORE 7

APPENDIX II: Prescreening eQuestionnaire

Date: _____

Mother

Name: (First and Last) _____

Relationship to Infant: ____Mother

Date of Birth: _____ (excluded if not ≥18 years of age)

Phone: (best # to call) _____

Best time of day to call: ____Morning ____Afternoon ____Evening ____Other *(open ended)*

Email: _____

Confirm Email: _____

Infant/Toddler

Name (First and Last) _____ Gender: ___Boy or ___ Girl

Date of Birth: _____ (excluded if not in age group 0-24 months at time of enrollment)

*The following is a questionnaire to help us better understand you and your child; this will help us determine if this study is right for you. Please pick the **best** answer choice.*

1. Do you or your child have a significant limitation (including medical or physical concerns, travel, etc.), which may interfere with daily study participation for 30 days in a row?
   a. Yes *(exclusion)*
   b. No
   c. Don't Know/Not Sure *(exclusion)*

2. Do you live in a household where you have an easy, reliable access, 24-hours per day to the internet, and do you also have one or more of the following electronic devices: tablet or smartphone?
   a. Yes
   b. No *(exclusion)*

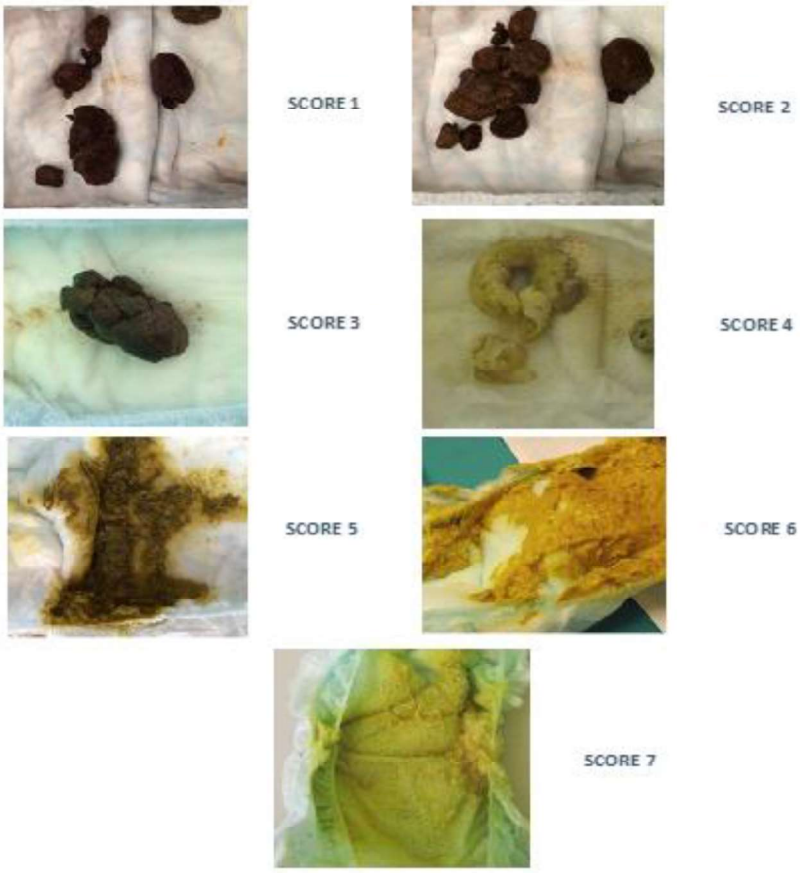
3. Is the smartphone or tablet being used to capture and upload images for this study more than 4 years old?
   a. Yes *(exclusion)*
   b. No

4. Are you now using, or are you willing to use, disposable diapers for your child?
   a. Yes
   b. No *(exclusion)*

5. Using the images below, please select: *(formatted as two questions in ClaimIt)*

    a. Your child's most frequent stool consistency

    b. Your child's **second** most frequent stool consistency



6. Does your child experience the following (liquid or hard stools) at least once a week?

SCORE 1

SCORE 2

SCORE 6

SCORE 7

a. Yes, both
b. Yes, liquid stools
c. Yes, hard stools
d. No

IF YOU HAVE ANY QUESTIONS OR PROBLEMS COMPLETING AND/OR SUBMITTING THIS QUESTIONNAIRE, PLEASE CALL US AT: 1-XXX-XXX-XXXX

APPENDIX III: Screening eQuestionnaire

Date: _____

Mother (Info below was also collected at prescreening, verify accuracy)

Name (First and Last): _____

Relationship to Infant: ____Mother

Date of Birth: _____ (excluded if not ≥18 years of age)

Phone: (best # to call) _____

Best time of day to call: ____Morning ____Afternoon ____Evening ____Other *(open ended)*

Address: (# and street) _____

(City, State, Zip Code)_____

Email: _____

Infant/Toddler (Info below was also collected at prescreening, verify accuracy)

Name (First and Last) _____ Gender: ___Boy or ___ Girl

Date of Birth: _____ (excluded if not in age group 0-24 months at time of enrollment)

*The following is a questionnaire to help us better understand you and your child; this will help us determine if this study is right for you. Please pick the **best** answer choice.*

1. Does your child consume standard food (breastmilk; formula; commercial/homemade baby, table or finger food) appropriate for their age?
   a. Yes
   b. No *(exclusion)*

2. Do you or your child have a significant limitation (including medical or physical concerns, travel, etc.), which may interfere with daily study participation for 30 days in a row?
   a. Yes *(exclusion)*
   b. No
   c. Don't Know/Not Sure *(exclusion)*

3. Do you live in a household where you have reliable, easy access to the internet and electronic devices such as a smartphone or tablet?
   a. Yes
   b. No *(exclusion)*

4. Is the smartphone/tablet being used capable of capturing and sending high quality electronic images?
   a. Yes
   b. No *(exclusion)*

5. What device will be used for capturing and transmitting high quality electronic images?
   _____ *(open ended question)*

IF YOU HAVE ANY QUESTIONS OR PROBLEMS COMPLETING AND/OR SUBMITTING THIS QUESTIONNAIRE, PLEASE CALL US AT: 1-XXX-XXX-XXXX

APPENDIX IV: Compliance eQuestionnaire

To be sent to participant when no image has been uploaded for >24 hours.

1. Did your child produce a stool in the last 24 hours?
   a. Yes
   b. No

   (If yes) Please remember that images should be taken and uploaded no longer than 10 minutes after your child has soiled the diaper, unless the stool was significantly smushed.

   (If no) Why did your child not have stool in the last 24 hours?
   _____Probably constipated _____I don't know _____Other (Open ended)

APPENDIX V: Parental Satisfaction with ClaimIt Platform

The following questions are regarding the use of the ClaimIt application during your participation in this clinical trial:

1. Please rate the ClaimIt application's overall ease of use on a scale of 1 to 5:

   (Very Difficult) 1 2 3 4 5 (Very Easy)

2. Did the ClaimIt application malfunction?

   a. Yes (will be asked a follow-up question)

   b. No

   If Yes, please describe what happened:

   _____

   _____

3. Have you participated in any other clinical study?

   a. Yes (will be asked a follow-up question)

   b. No

   (If yes) What did you prefer about study participation using the ClaimIt application? Why?

   _____

   _____

   (If yes) What did you prefer about participation in the previous study? Why?

   _____

   _____

4. Do you have any comments about using the application (favorable or unfavorable) that you would like the PIs to know?

   _____ (Open ended question)

5. Did you find it difficult to score the stool pictures?
   a. Yes
   b. No

   (If yes) Why?

   a. Because the app was not easy to use to see the example pictures
   b. Because it was not easy for me to score the stool, even with the example pictures provided
   c. Because sometimes the stool seemed in between two examples
   d. Because I did not have the time to make a decision
   e. Other _____ *(Open ended question)*

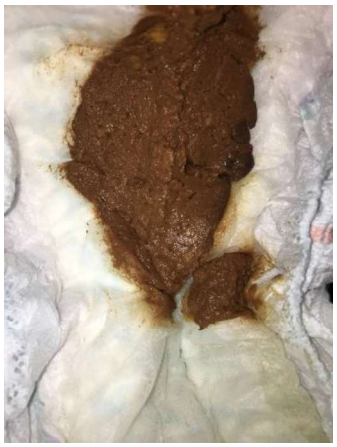
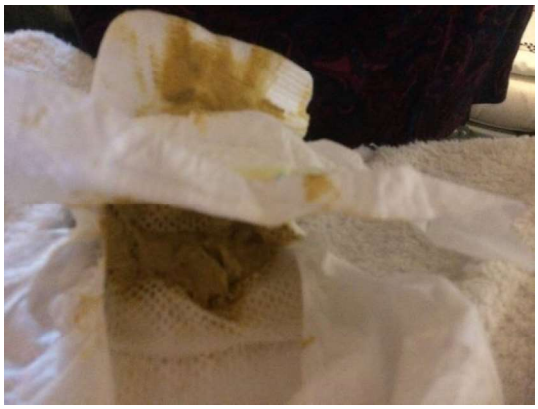
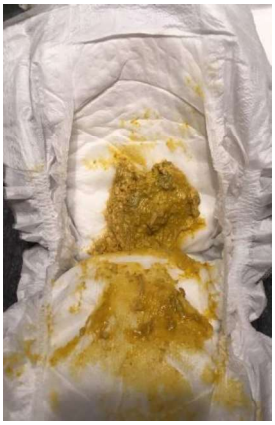
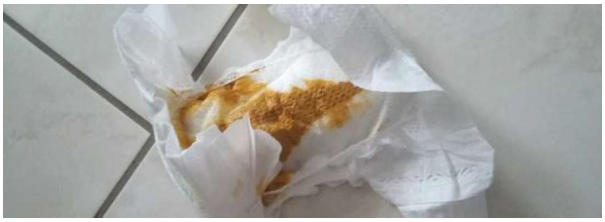
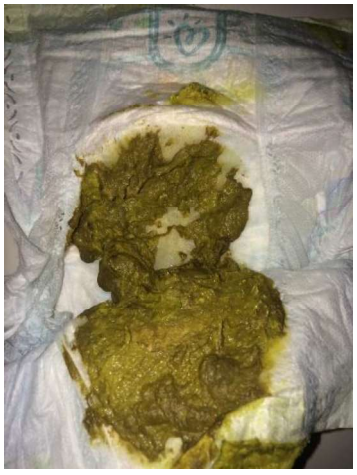
6. If the doctor wanted to know about your child's stool type, do you feel it would be helpful to have an automatized tool to score the stool pictures for you?
   a. Yes
   b. No

7. Would you say your child's stool pattern is, or was, a concern to you?
   a. Yes, frequently
   b. Yes, when my baby was younger
   c. No, never

8. Was it easy to take the pictures of the diaper?
   a. Yes
   b. No

   (if no) Why? _____

APPENDIX VI: Good/Bad Stool Image Examples

Good	Bad
	
	
	

Protocol Danone Stool V2 12OCT2018

Final Audit Report 2019-06-20

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