HRP-591 - Protocol for
Human Subject Research

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Califormula Study: Calibrated Formula Feeding to Optimize Infant Growth

Principal Investigator:

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Version Date:

Provide a version date for this document. This date must be updated each time this document is submitted to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

September 29, 2021

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual", under "ClinicalTrials.gov" for more information.

NCT05104073

Important Instructions for Using This Protocol Template:

This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.

1. **GENERAL INSTRUCTIONS:**
   - Prior to completing this protocol, ensure that you are using the most recent version by verifying the protocol template version date in the footer of this document with the current version provided in the CATS IRB Library.
   - Do not change the protocol template version date located in the footer of this document.
   - Some of the items may not be applicable to all types of research. If an item is not applicable, please indicate as such or skip question(s) if indicated in any of the instructional text.
   - **GRAY INSTRUCTIONAL BOXES:** Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.
     - **Do NOT delete the instructional boxes from the final version of the protocol.**
   - Add the completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page.

2. **CATS IRB LIBRARY:**
   - Documents referenced in this protocol template (e.g. SOP's, Worksheets, Checklists, and Templates) can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

3. **PROTOCOL REVISIONS:**
   - When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the guides available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

- Update the Version Date on page 1 each time this document is submitted to the IRB office with revisions.

If you need help…

All locations:
Human Research Protection Program
Office for Research Protections
The 330 Building, Suite 205
University Park, PA 16802-7014
Phone: 814-865-1775
Fax: 814-863-8699
Email: irb-orp@psu.edu
https://www.research.psu.edu/irb

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1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

This pilot study seeks to determine if formula feeding recommendations that are calibrated using age and weight specific caloric intake recommendations can prevent excessive infant weight gain and reduce overweight in the first 6 months after birth among infants born to mothers with overweight prior to pregnancy electing to exclusively formula feed their infants. Calibrated formula feeding refers to adjusting the recommended daily caloric formula intake to account for weight status. A cohort of 60 infants will be recruited and randomized 2-3 weeks after birth to an intervention arm characterized by calibrated formula feeding recommendations or a control group with ad lib feeds as per usual care. Intervention group parents will also be given written instructions on infant hunger and satiety cues as well as copies of videos with guidance on bottle feeding and how to soothe fussy infants without feeding. We hypothesize that the calibrated formula intake intervention will reduce rapid infant gain and overweight during infancy resulting in lower weight-for-length at age 6 months.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

- Conditional Weight Gain between Birth and Age 6 months

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

- Conditional Weight Gain during the intervention period spanning Ages 1-6 Months
- Mean Weight-for-Length Z-score (WLZ) at Age 6 Months
- Growth Trajectory during the intervention period spanning Ages 1-6 Months (repeated measures of weight-for-length)
- Proportion of Infants with Overweight (Weight-for-Length ≥95th Percentile on WHO Growth Charts) at Age 6 months
- Feasibility: a) recruitment, b) ability to give tailored formula volume recommendations, c) visit completion, d) retention through 6 months
- Acceptability: parent adherence to formula volume recommendations as measured by 3 day feeding diaries at 2, 3, 4, 5, and 6 months for the intervention group

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the study procedure is available to patient without taking part in the study.

Infant obesity predicts childhood and adult obesity,[1-6] as the highest quintile of weight gain between birth and 5 months of age doubles the odds of overweight at 4.5 years.[1] Although familial lifestyle and environmental factors may contribute to the epidemic,[7-9] we propose that developmental programming effects of the maternal environment during in utero and newborn periods result in early onset and persistent overweight/obesity (OW/OB).

What are the mechanisms that account for this generational cycle of OB and critical fetal/newborn periods? Increased *energy intake*, not reduced energy expenditure, largely explains population weight gain in children and adults.[10-13] Even a small mismatch (<0.5%) in intake/expenditure will lead to weight gain over time.[14] Thus, the combination of appetite/satiety and the energy content of foods represent a critical regulator of energy intake and OB in both adults and infants. As described below, we propose that programmed offspring hyperphagia combined with feeding of high caloric value breast milk or infant formula potentiates early life accelerated weight gain and the cycle of OW/OB.

Programmed Offspring Hyperphagia: During pregnancy maternal OW/OB impacts fetal brain development leading to a diversity of offspring neurodevelopmental disorders (e.g., cognitive, neurodegenerative)[15-17] among which hyperphagia-induced OB may be the most recognizable. Maternal body mass index (BMI) is correlated with fetal and infant weight gain. Mothers with OW/OB have an increased risk of large for gestational age (LGA) newborns,[18] which have a >2-fold risk of preschool OB[19] and adult metabolic syndrome.[20-28] The importance of the pregnancy environment is evidenced by the finding that children of mothers with OB who have undergone bariatric surgery are three-times less likely to be severely obese when compared to siblings born prior to surgery.[29] Furthermore, the critical role of maternal OW/OB is evidenced by the finding that paternal OB is associated with a four-fold increased risk of OB in daughters at age 18 years, while maternal OB results in an eight-fold increased risk.[9]

Animal studies have replicated evidence of human programmed obesity. In mice, offspring of OB, high fat diet rodents are predisposed to newborn OW and adult OB,[30,31] and a spectrum of neurologic disorders.[32-35] Within the hypothalamus, the maternal OW/OB nutritional environment alters neural cellular and epigenetic signaling that result in increased appetite and reduced satiety gene expression and neurons. Laboratory studies have demonstrated that maternal OB (and high fat diet) increases offspring hypothalamic neuronal peptides and orexigenic neurons,[36-39] and programs offspring hyperphagia.[30,36,40-43] Maternal OB reduces offspring pro-opiomelanocortin (POMC) expression with an increase in arcuate neuropeptide Y (NPY) signaling,[44] while offspring born to dams fed a high-carbohydrate diet demonstrate increased NPY release.[45] In rodents, offspring of obese dams exhibit decreased hypothalamic tissue expression of select neurogenic signal factors (Ngn3 and Mash1) which regulate neural progenitor cell differentiation to appetite vs satiety neurons, consistent with increased arcuate agouti-related peptide (AgRP) and reduced POMC expression.[36,46] Maternal OB reduces offspring Mash1 mRNA expression and increases NPY neurons.[38] With evidence of programmed neurogenesis and hyperphagia, OW/OB LGA human and mouse offspring gain weight more rapidly than appropriate for gestational age (AGA) offspring.

What can be done: Despite these findings, effective interventions short of bariatric surgery to break the generational cycle of OB are limited to those promoting responsive parenting behavioral interventions.[47,48] Although maternal lifestyle interventions and exclusive breastfeeding are optimal for many reasons, reports suggest limited efficacy at preventing obesity among offspring. Randomized studies have attempted pre-pregnancy weight loss or controlled gestational weight gain, also with limited effects on neonatal body composition.[49-52] Although neonatal care has incorporated nutrient fortification to preterm, low birth weight newborns to augment weight gain,[53] there have been no studies calibrating intake to prevent excess weight gain among term newborns at risk of OW/OB.

We propose several discrete benefits of calibrated formula feeding recommendations that are age and weight-status specific to promote healthy newborn growth. The prevention of OW infants at 6 months of age would be predicted to reduce the rate of childhood and even adult OB. This may occur, in part, by preventing OB-associated leptin resistance. Thus, preventing the onset of infant OB,

hyperleptinemia and leptin resistance[54-57] may normalize appetite throughout childhood. Further, consistent with evidence in animal models, calibrated intake and newborn growth may potentially reprogram the newborn hypothalamic arcuate nucleus, correcting the appetite/satiety neuronal ratio.[58-61] In this project, we will examine the potential efficacy of a novel preventive strategy to normalize infant weight gain to prevent the development of infant OW and interrupt the cycle of OB.

2.2 Previous Data

Describe any relevant preliminary data.

N/A

2.3 Study Rationale

Provide the scientific rationale for the research.

Infancy is a critical period of developmental plasticity with lasting metabolic and behavioral consequences.[62] Obesity is an outcome that is affected by this plasticity during infancy. The obesity epidemic is a public health crisis that will severely impact US children across their lifecourse and place a substantial burden on our healthcare system. Nearly 1 in 5 US children aged 2-19 are obese, and ~1 in 3 are overweight (BMIs ≥95th and 85th percentiles, respectively).[63,64] For many children, this problem begins early as 23% of 2-5 years olds are already overweight[64] and 9-14% are already obese.[63,65] Primary prevention is likely the best solution, as recent simulation data in the *New England Journal of Medicine* suggest that "a 2 year old who is obese is more likely to be obese at 35 years of age than an overweight 19 year old."[66]

Though somewhat controversial, there is evidence that formula feeding is associated with a modestly increased risk obesity[67-71] and rapid infant weight gain,[72] with further evidence that the volume of formula consumed, overfeeding, an important contributor to excess weight gain[73,74] as might be expected. Similar findings have been reported for bottle feeding.[75] Adjusting or calibrating the recommended amount of formula across the first 6 months after birth shows promise as a strategy to reduce rapid infant weight gain and early life overweight.[74]

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review "HRP-416- Checklist - Children"
- **Pregnant Women** – Review "HRP-412- Checklist - Pregnant Women"
- **Cognitively Impaired Adults-** Review "HRP-417- Checklist - Cognitively Impaired Adults"
- **Prisoners-** Review "HRP-415- Checklist - Prisoners"
- **Neonates of uncertain viability or non-viable neonates-** Review "HRP-413- Checklist - Non-Viable Neonates" or "HRP-414- Checklist - Neonates of Uncertain Viability"

[Do not type here]

3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.)

1. Term or Early Term (≥37 weeks), singleton infants
2. Infant birthweight ≥50th percentile based on the 2013 Fenton Growth Charts (which account for sex of child and gestational age at birth)
3. Infant without substantial neonatal morbidity that would affect feeding or weight gain (e.g. known chromosomal abnormality, metabolic disorder, cleft lip/palate, etc.)
4. Infant age ≤1 month
5. Mothers with pre-pregnancy body mass index ≥25 kg/m^2
6. Mothers ≥18 years old
7. Parental plan to exclusively feed infant 19-20 kcal/ounce formula upon delivery or by the start of the intervention period ~1 month after delivery
8. Parental intention to have infant well child visits through age 6 months at a Division of Academic General Pediatrics practice site (Hope Drive, Elizabethtown, Nyes Road)
9. English speaking parent

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

1. Infants who weigh less than their birthweight 21 days after delivery

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

1. Infants exhibiting failure-to-thrive defined as:
    a. Weight-for-length <5th percentile for sex and age on the WHO growth chart
    b. Downward crossing of >2 major centile lines on the WHO growth chart (relevant major lines include 95th, 90th, 75th, 50th, 25th, 10th, 5th) after enrollment
2. Non-adherence to the study visit schedule characterized by failing to complete **two** scheduled study intervention visits within 2 weeks of turning 1, 2, 3, 4, and 5 months old (does not include enrollment and final visit)

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

Study personnel will contact consenting parents by phone notifying them of their removal from the study and the reason for withdrawal. If the reason is due to failure-to-thrive, the infant's pediatrician will also be notified. If study personnel are unable to reach the consenting parent, a letter will be sent via US mail.

No further data will be collected on participants that are withdrawn, and these participants will not be replaced.

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (http://irb.psu.edu). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (http://studyfinder.psu.edu) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (http://irb.psu.edu).

[Do not type here]

4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, include this method in this section.
- Information provided in this protocol needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form on in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, What is appropriate for study recruitment?" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

Participants will be identified during the birth hospitalization at Penn State Hershey Children's Hospital and through newborn visits at a practice site within the Division of Academic General Pediatrics (offices at Hope Drive, Elizabethtown, Nyes Road) via review of birth hospitalization and neonatal electronic medical records.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

[Do not type here]

4.2.1 How potential subjects will be recruited.

Parents of eligible neonates will be given information regarding the opportunity to participate by research staff during the birth hospitalization or at a pediatric clinic during the first weeks after birth.

4.2.2 Where potential subjects will be recruited.

1. Penn State Hershey Children's Hospital
2. Penn State Hershey Division of Academic General Pediatrics practice sites (Hope Drive, Elizabethtown, Nyes Road)

4.2.3 When potential subjects will be recruited.

Participants will be recruited and consented during the birth hospitalization or during routine outpatient visits within the first month after birth

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB.

[*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Participants will first be screened through review of their electronic medical record to determine potential eligibility.

5.0 Consent Process and Documentation

Refer to the following materials:

- The "HRP-090- SOP - Informed Consent Process for Research" outlines the process for obtaining informed consent.
- The "HRP-091– SOP - Written Documentation of Consent" describes how the consent process will be documented.
- The "HRP-314- Worksheet - Criteria for Approval" section 7 lists the required elements of consent.
- The "HRP-312- Worksheet - Exemption Determination" includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu). Links to Penn State's consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

[Do not type here]

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

The following checkbox is for all locations EXCEPT Penn State Health and College of Medicine:

☐ **Exempt Research at all Locations Except Penn State Health and the College of Medicine: If you believe that the research activities outlined meet one or more of the criteria outlined in "HRP-312- Worksheet- Exemption Determination." Please verify by checking this box that if conducting an exempt research study, the consent process will disclose the following (all of which are included in "HRP-590- Consent Guidance for Exempt Research"):**

Penn State affiliation; name and contact information for the researcher and advisor (if the researcher is a student); the activities involve research; the procedures to be performed; participation is voluntary; that there are adequate provisions to maintain the privacy interests of subjects and the confidentiality of the data; and subjects may choose not to answer specific questions.

If the research includes the use of student educational records include the following language in this section (otherwise delete): The parent or eligible student will provide a signed and dated written consent that discloses: the records that may be disclosed; the purpose of the disclosure; the party or class of parties to whom the disclosure may be made; if a parent or adult student requests, the school will provide him or her with a copy of the records disclosed; if the parent of a student who is not an adult so requests, the school will provide the student with a copy of the records disclosed.

Note: If this box has been checked, skip the remainder of section 5 and proceed to section 6 of this protocol. If the investigator's assessment is inaccurate, an IRB Analyst will request revision to the protocol and that an informed consent form be submitted for review and approval. Except for exemptions where Limited IRB Review (see "HRP-312- Worksheet- Exemption Determination") is required or where otherwise requested by the IRB, informed consent forms for research activities determined to be exempt without Limited IRB Review are generally not required to be submitted for review and approval by the University Park IRB.

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Consent will be obtained from eligible parents within the first month of childbirth. It can occur on the maternity floors of Penn State Health Children's Hospital or at outpatient clinics where Division members from Academic General Pediatrics practice (Hope Drive, Elizabethtown, Nyes Road).

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Parents will be reassured that participation in the study is completely optional and will not affect the care that their child receives regardless of the decision to participate or not.

5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

5.3.1 Indicate which of the following conditions applies to this research:

☐ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

N/A

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

N/A

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.4.1 Indicate the elements of informed consent to be omitted or altered

N/A

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

N/A

5.4.3 Describe why the research involves no more than minimal risk to subjects.

N/A

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

Participants will not be debriefed at the end of the study as parents will already receive information on their child's growth from the infant's pediatrician.

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

N/A

5.5.2 Describe why the research involves no more than minimal risk to subjects.

N/A

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation. If not applicable, indicate "not applicable."

N/A

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review "HRP-

091 –SOP- Written Documentation of Consent" and "HRP-103 -Investigator Manual" to ensure that you have provided sufficient information.

N/A

5.6.2 Cognitively Impaired Adults

Refer "HRP-417 -CHECKLIST- Cognitively Impaired Adults" for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

N/A

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 - SOP- Legally Authorized Representatives, Children, and Guardians."

N/A

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

N/A

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Parental permission will be obtained through the written consent. Parents will provide consent for study participation.

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

The children involved are infants and will not be old enough to assent during the course of the study.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

[Do not type here]

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

All identifiable data will be destroyed after all publications have been published and the study is closed.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

A partial waiver for uses and disclosures of PHI is required for the practical conduction of this research. The waiver will allow team members involved in recruitment to access electronic medical records of patients who meet basic inclusion criteria. This will save time and protect privacy for non-eligible families.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

Without review of potential participants' medical records prior to study explanation would result in non-eligible families being approached for the research. This would cause an unnecessary invasion of privacy for families that would not be able to participate.

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (http://irb.psu.edu). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions)

[Do not type here]

7.1 Study Design

Describe and explain the study design.

This study is a randomized, clinical trial involving 60 exclusively formula fed infants born at ≥37 weeks gestational age who are at-risk for overweight based upon maternal pre-pregnancy overweight or obesity (or alternatively at first prenatal visit if pre-pregnancy weight/height not known) and infant birthweight ≥50th percentile. Infants will be enrolled at Penn State Health Children's Hospital or at affiliated clinics within the Division of Academic General Pediatrics between birth and age 1 month, where they will be randomized to a calibrated formula intake intervention or control. Participating infants in the intervention group will be seen monthly until age 6 months where they will be weighed and measured, and parents will complete surveys related to volume of formula consumed, infant appetite, parent feeding style, and infant temperament. Control infants will follow the same procedures, but will not have scheduled visits at ages 3 and 5 months. Instead their visits will correspond to usual care well child visits at ages 1, 2, 4, and 6 months.

7.2 Study Procedures

Provide a step by step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.)

- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

Prior to enrollment, infants will be screened by study coordinators to ensure eligibility consistent with study inclusion/exclusion criteria.

7.2.1 Visit 1

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

Birth – infant age 1 month: Parents will then review and complete the informed consent document during the birth hospitalization or at a clinic visit allowing for continued participation. Demographic data will be collected from parent-completed surveys on Redcap. Study coordinators will review the electronic medical record to obtain data related to pregnancy and birth history (e.g. birthweight, gestational age, maternal pre-pregnancy BMI, etc.). Additionally, parent contact information will be obtained.

Anthropometrics – if enrollment occurs during the birth hospitalization, birth weight and birth length will be recorded from the electronic medical record. If enrollment occurs at an outpatient clinic visit, the following procedures will be used (and for all subsequent weights and lengths):

- Weight – will be measured to the nearest 0.001 kg using a calibrated, digital electronic scale
- Recumbent Length – will be measured to the nearest 0.1 cm using a portable stadiometer (Shorr)

Diary card - Parents will be given a diary card to record volume of infant formula consumed for the 3 days prior to the 1 month well child visit (Visit 2) and all subsequent visits. Instructions for the diary card will ask parents:

a) Volume consumed in each feeding for the day (volume is the amount that passes the infant's lips – if formula is spit-up, it still counts as having been consumed)
b) Type of infant formula
c) Size of bottle used
d) Other sources of nutrition (e.g. juice, water, foods)

Randomization – following the visit, infants will be randomized to intervention or control using a computer-generated randomization program generated by a statistician not affiliated with the trial. Randomization will include stratification for sex of the infant (male/female) and maternal pre-pregnancy BMI category (25-29.9 kg/m^2 vs. ≥30 kg/m^2).

7.2.2 Visit 2

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

Age 1 Month Visit (ages 24 – 41 days)

Both study groups:

1. Anthropometrics of infant (weight, recumbent length)
2. Parent-completed Surveys
    a. Baby Eating Behavior Questionnaire[76]
    b. Babies Basic Needs Questionnaire

c. Single item adapted from the Infant Feeding Practices Study II[77]:"I encourage my infant to finish his or her bottle of formula"[78]; responses include:
Never ..... … Rarely..... … Sometimes ..... … Most of the time ..... … Always..... …

3. Diary cards to be completed for the 3 days following the visit
4. Diary cards to be completed x 3 days prior to next study visit

Intervention group only:

1. Parents will be provided with handouts on hunger/satiety cues and calming a fussy baby
2. Parents will be given a digital streaming copy of the video, "Happiest Baby on the Block" available at: https://www.happiestbaby.com/products/baby-streaming-video-english
3. Parents will be given a copy of a video demonstrating responsive bottle feeding: https://youtu.be/NLnPGJKdPUw [78]
4. Parents will be given a copy of Bottle Feeding Basics video: https://360.articulate.com/review/content/99a63b9a-184c-474e-b836-7d8cd8aa1652/review
5. Study coordinators will provide parents with a range of formula volume to be consumed based upon research conducted by Butte:[79]

Table 8 Energy requirements for formula-fed infants 0–12 months of age

Age (months)	Weight (kg)[a]	Weight velocity (g day^{-1})[b]	Total energy expenditure (kJ day^{-1})	Total energy expenditure (kcal day^{-1})	Energy deposition (kJ day^{-1})	Energy deposition (kcal day^{-1})	Energy requirement (kJ day^{-1})	Energy requirement (kcal day^{-1})	Energy requirement (kJ kg^{-1} per day)	Energy requirement (kcal kg^{-1} per day)
Boys										
1	4.58	35.2	1462	349	884	211	2345	560	512	122
2	5.5	30.4	1779	425	764	183	2543	608	462	111
3	6.28	23.2	2049	490	582	139	2631	629	419	100
4	6.94	19.1	2277	544	224	53	2501	598	360	86
5	7.48	16.1	2464	589	189	45	2653	634	355	85
6	7.93	12.8	2619	626	150	36	2770	662	349	83
7	8.3	11.0	2747	657	69	17	2816	673	339	81
8	8.62	10.4	2858	683	65	16	2923	699	339	81
9	8.89	9.0	2951	705	57	14	3008	719	338	81
10	9.13	7.9	3034	725	89	21	3123	746	342	82
11	9.37	7.7	3117	745	87	21	3204	766	342	82
12	9.62	8.2	3203	766	93	22	3296	788	343	82
Girls										
1	4.35	28.3	1382	330	746	178	2128	509	489	117
2	5.14	25.5	1655	396	672	161	2327	556	453	108
3	5.82	21.2	1890	452	559	134	2449	585	421	101
4	6.41	18.4	2094	500	285	68	2379	569	371	89
5	6.92	15.5	2270	543	239	57	2510	600	363	87
6	7.35	12.8	2419	578	199	47	2617	626	356	85
7	7.71	11.0	2543	608	83	20	2626	628	341	81
8	8.03	9.2	2654	634	69	17	2723	651	339	81
9	8.31	8.4	2751	657	63	15	2814	673	339	81
10	8.55	7.7	2834	677	74	18	2908	695	340	81
11	8.78	6.6	2913	696	63	15	2976	711	339	81
12	9	6.3	2989	714	60	14	3049	729	339	81

[a]50th percentile weight for age of the WHO pooled breast-fed data set[36].
[b]50th percentile weight increment of the WHO pooled breast-fed data set[36].

Recommended formula volumes will be calculated based on data from the table above informing parents of the recommended formula volume based on 19/20 kcal/ounce formula at the infant's current age as well as the anticipated volume at the infant's next visit as described below.

For those with weight-for-length (WFL) <75th percentile on the WHO WFL growth chart, recommended daily formula volumes will be calculated based upon the infant's sex, current age, weight, and energy requirement (kcal/kg/day). Further, parents will be informed of the volume to expect at the subsequent visit in one month should the child maintain the same weight-for-age percentile.

For those with WFL ≥75th percentile on the WHO WFL growth chart, recommended daily formula volumes will be calculated based upon the child's current age, weight, and energy requirement (kcal/kg/day) with a 10% reduction in daily volume. Further, parents will be

informed of the volume to expect at the subsequent visit in one month should the child maintain the same weight-for-age percentile, again with a 10% reduction.

10% was chosen for this pilot because it balances feasibility (relatively likely that parents can comply) and safety (unlikely to cause failure-to-thrive by reducing total daily formula volume by ~3 ounces)

6. Parents will be given instruction to prepare the formula volume in each bottle on the lower end of what they anticipate the infant will eat. For example, if they anticipate the infant will consume 3-4 ounces per feed, they will prepare 3 ounces at first. If hunger cues persist, they will then prepare an additional 1-2 ounces of formula.

7.2.3 Visit 3

Age 2 Month Visit (42-77 days)

Both study groups:
1. Anthropometrics of infant (weight, recumbent length)
2. Diary cards to be completed for the 3 days following the visit
3. Diary cards to be completed x 3 days prior to next study visit

Intervention group only:
1. Recommend formula volumes for the next month based on Visit 2 procedures
2. **If, for a second consecutive month, the child has WFL ≥75th percentile on the WHO WFL growth chart**, recommended daily formula volumes will be calculated based upon the child's current age, weight, and energy requirement (kcal/kg/day) with a 15% reduction in daily volume. Further, parents will be informed of the volume to expect at the subsequent visit in one month should the child maintain the same weight-for-age percentile, again with a 15% reduction.

7.2.4 Visit 4

Age 3 Month Visit (78-109 days): Intervention group only

1. Anthropometrics of infant (weight, recumbent length)
2. Diary cards to be completed for the 3 days following the visit
3. Diary cards to be completed x 3 days prior to next study visit
4. Recommend formula volumes for the next month based on Visit 2 and 3 procedures

7.2.5 Visit 5

Age 4 Month Visit (110-140 days)

Both study groups:
1. Anthropometrics of infant (weight, recumbent length)
2. Diary cards to be completed for the 3 days following the visit
3. Diary cards to be completed x 3 days prior to next study visit

Intervention group only:
4. Recommend formula volumes for the next month based on Visit 2 and 3 procedures

5. Provide handouts on soothing fussy infants, feeding

7.2.6 Visit 6

Age 5 Month Visit (141-171 days) – Intervention Group Only

1. Anthropometrics of infant (weight, recumbent length)
2. Diary cards to be completed for the 3 days following the visit
3. Diary cards to be completed x 3 days prior to next study visit
4. Recommend formula volumes for the next month based on Visit 2 and 3 procedures

7.2.7 Visit 7

Age 6 Month Visit (172-210 days)

Both study groups:

1. Anthropometrics of infant (weight, recumbent length)
2. Parent completed surveys
    a. Baby Eating Behavior Questionnaire
    b. Infant Feeding Styles Questionnaire
    c. Baby's Basic Needs Questionnaire
    d. Infant Behavior Questionnaire

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Participants will be enrolled in the study for 6 months. Most study visits will occur in conjunction with regular well child care, adding ~15 minutes to each visit.

8.0 Number of Subjects and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. Distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures if applicable (i.e., numbers of subjects excluding screen failures.)

For this pilot study, 60 infants will be recruited. We believe that this number of infants who meet the inclusion/exclusion criteria can feasibly be recruited over a 6 month period.

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

The sample size for this pilot study is based upon the number of participants that we felt we could feasibly recruit given the time and resources available for recruitment. As this pilot is going to determine feasibility, 60 participants should be adequate. Further, we will use the data generated to determine the sample size necessary for a fully powered subsequent trial.

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

We will assess conditional weight gain from birth to 6 months to assess rapid infant growth.[80,81] Conditional weight gain will be calculated as standardized residuals from the linear regression of weight for age at 6 months on weight for age at birth, with length for age at birth and 6 months and infant age at the 6-month visit entered as covariates. We will explore the moderating role of child sex, delivery mode, and maternal parity on intervention effects. Similar analyses will be conducted for the intervention period spanning ages 1-6 months.

For cross-sectional analyses at age 6 months, ANOVA will estimate the effects of intervention group on mean weight-for-length. Logistic regression will be used to compare intervention effects on the dichotomous outcome of overweight at 6 months.

For growth from 1-6 months, we will fit a repeated measures ANOVA of BMI, with visit and study group as within and between factors, respectively.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as not applicable.

[Do not type here]

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Growth charts will be reviewed in real time at patient visits. Those meeting criteria for growth failure (failure-to-thrive) described above will be immediate flagged and discussed with Dr. Paul.

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

For this 6 month trial, growth charts are the data that will be reviewed.

9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Any growth failure event will be considered an adverse event, and these will be captured with a case report form.

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Data are collected per the visit schedules for the intervention and control groups.

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

The study coordinators and PI will be the ones reviewing the data.

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Cumulative data will be reviewed at the end of the trial.

9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

As we expect adverse events to be infrequent, we are not planning to do any interim safety analyses.

9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Suspension of the research would occur if:

1. >33% of participants are not adhering to the data collection procedures
2. >33% of intervention group participants meet criteria for failure-to-thrive
3. Attrition exceeds 33% after Visit 2

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. Note: Loss of confidentiality is a potential risk when conducting human subject research.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

It is possible that a reduction in formula intake could lead to temporary growth faltering (i.e. failure-to-thrive), though this would be self-limited and could be addressed by subsequently increasing formula intake.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 13.0.

The study intervention could improve infant growth trajectories, reduce rapid infant weight gain, and reduce likelihood of overweight during infancy and beyond for participants.

11.2 Potential Benefits to Others

Include benefits to society or others.

This pilot could inform formula feeding guidelines for infants in clinical care and in clinical research trials.

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

Parents of individual participants will receive real-time data on their infant's growth, consistent with clinical care.

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

Participating parents randomized to the intervention group will receive up to $300 for participation in the study; control participants who have 2 less study visits will receive up to $250 for participation. Following Visit 2, they will receive $50 for successful completion of the visit and study surveys. $25 will be given following visits 3-6 (note no visit 4 and 6 for controls). Upon completion of Visit 7's anthropometrics and survey data collection, participants will receive $150.

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

Research participants will not accrue any additional costs as a result of their participation.

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

This research will be conducted on the maternity/nursery floors of Penn State Children's Hospital and at the ambulatory clinics affiliated with the Division of Academic General Pediatrics.
Penn State Children's Hospital maternity/nursery floors - ~2000 infants are delivered annually on the floor. All mother-baby dyads on the well newborn service have private rooms. Recruitment and enrollment procedures are expected to occur frequently on this unit (6^{th} and 7^{th} floors).
Ambulatory Clinics – The Division of Academic General Pediatrics performs >50,000 visits annually at its clinics located at Hope Drive, Elizabethtown, and Nyes Road. These clinics are accustomed to research. Recruitment and enrollment may also occur at the clinics, and monthly anthropometrics and data collection will occur, typically as part of well child care visit.

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

With ~2000 well newborns delivered annually, it is expected that ~30% will be exclusively formula fed. Among these 600, it is expected that ~200-300 will meet the remaining inclusion/exclusion criteria, providing an ample pool of participants.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

Dr. Paul has a long track-record of conducting clinical research and devoting appropriate time to his research studies despite other obligations including patient care and administration.

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study, if applicable.

Participating infants will receive their typical infant well child care from their pediatricians.

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

All study team members will have completed the appropriate training prior to the initiation of the study. Team meetings will occur at least monthly via Zoom.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

N/A

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

☐ St. Joseph Administrative Review – **Penn State Health only** – Penn State Health Research that will be conducted at St. Joseph Medical Center or St. Joseph Community Medical Groups.

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and the Penn State PI is the lead investigator, describe the processes to ensure communication among sites in the sections below.

[Do not type here]

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

N/A

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

N/A

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

N/A

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

N/A

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

N/A

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

N/A

18.0 Adverse Event Reporting

18.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Auditing and Inspecting

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for future **undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

[Do not type here]

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

Files will be stored on the IT file server (hersheymed.net\files). We will also be utilizing Penn State's RedCap EDC system to store all study data.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Files will be stored on the IT file server (hersheymed.net\files). We will also be utilizing Penn State's RedCap EDC system to store all study data.

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate as such.

5 years following the completion of the study.

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

The investigators and the study sponsor.

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

N/A

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

N/A

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

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22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

For research being conducted at Penn State Health or by Penn State Health researchers only: The research data security and integrity plan is submitted using "HRP-598 – Research Data Plan Review Form."

Refer to Penn State College of Medicine IRB's "Standard Operating Procedure Addendum: Security and Integrity of Human Research Data," which is available on the IRB's website. In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all sub-sections of section 22.

For all other research: complete the following section. Please refer to PSU Policy AD95 for information regarding information classification and security standards and requirements. It is recommended that you work with local IT staff when planning to store, process, or access data electronically to ensure that your plan can be

carried out locally and meets applicable requirements. If you have questions about Penn State's Policy AD95 or standards or need a consultation regarding data security, please contact security@psu.edu.

See the Research Data Plan Review Form

CONSENT FOR RESEARCH
Penn State College of Medicine
Penn State Health

Title of Project:	Califormula Study: Calibrated Formula Feeding to Optimize Infant Growth
Principal Investigator:	Ian M. Paul, MD, MSc
Address:	500 University Drive Hershey, PA 17033
Telephone Numbers:	Weekdays: 8:00 a.m. to 5:00 p.m. (717) 531-5656. After hours call (717) 531-8521. Ask for the Pediatrics doctor on 24-hour call.

Subject's Printed Name: _____

We are asking you to be in a research study.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you, and there will be no penalty or loss of benefits to which you are entitled.

This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.

Some of the people who are eligible to take part in this research study may not be able to give consent because they are less than 18 years of age (a minor). Instead we will ask their parent(s)/guardian(s) to give permission for their participation in the study, and we may ask them to agree (give assent) to take part. Throughout the consent form, when we say "you", we mean you or your child.

KEY INFORMATION

The following is a short summary of this study to help you decide whether or not to be a part of this research. More detailed information is provided later in this form. If you have any questions, be sure to ask the study team.

Why am I being invited to take part in this research study?

We are asking you to take part in this voluntary research study because we are trying to learn how to promote optimal growth for exclusively formula fed babies for mothers with a pre-pregnancy body mass index of 25 or more.

What is the purpose of this research study?

The purpose of this voluntary research study is to determine if calibrated formula feeding recommendations can promote optimal growth for the first 6 months after birth for mothers with a pre-pregnancy body mass index of 25 or more. .

How long will the research study last?

Your participation in this study will last approximately 6 months.

What will I need to do?
Participating infants in the intervention group will be seen monthly until age 6 months where they will be weighed and measured, and parents will complete surveys related to volume of formula consumed, infant appetite, parent feeding style, and infant temperament. Control group infants will follow the same procedures, but will not have scheduled visits at ages 3 and 5 months. Instead their visits will correspond to well child clinic visits at ages 1, 2, 4, and 6 months.

What are the main risks of taking part in the study?
For this study, the main risks to know about are: There is an unlikely risk that a reduction in formula intake could lead to temporary growth faltering (i.e. failure-to-thrive), though this would be self-limited and could be addressed by subsequently increasing formula intake. There is also a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

What are the possible benefits to me that may reasonably be expected from being in the research?
We cannot promise any benefits to you from taking part in this study. However, possible benefits include the improvement of infant growth trajectories, reduction of rapid infant weight gain, and reduction of the likelihood of overweight during infancy and beyond for participants. Results of the study may benefit other people in the future by helping us learn more about formula feeding guidelines for infants at risk of becoming overweight.

What happens if I do not want to be in this research?
Participation in research is completely voluntary. You can decide to participate or not to participate.
You may choose not to take part in this research study.

DETAILED INFORMATION
The following is more detailed information about this study in addition to the information listed above.

1. Why is this research study being done?
This research is being done to find out if formula feeding recommendations that are calibrated using age and weight specific caloric intake recommendations can prevent excessive infant weight gain and reduce overweight in the first 6 months after birth among infants born to mothers with a pre-pregnancy body mass index of 25 or more electing to exclusively formula feed their infants.

Approximately 60 people will take part in this research study at Penn State Health.

2. What will happen in this research study?
If you agree to be in this research, you will first review and sign this consent form before any research procedures or tests are performed. You will be given a copy of the signed consent form for your records.

Research Procedures and Data Collection:
Visit 1: Birth – 1 month of age
This visit will occur during the birth hospitalization or at an outpatient clinic prior to the 1 month well child visit.

- Your child's weight and length will be obtained and recorded for the research.

- You will be asked for demographic data through an electronic REDCap survey.
- A study team member will obtain your contact information.
- You will be given a diary card to record volume of infant formula consumed for the three days prior to the 1 month well child visit (Visit 2) and all subsequent visits.

Visit 2: 1 Month Visit (24-41 days)

- Your child's weight and length will be obtained and recorded for the research.
- You will be asked some survey questions;
    - Baby Eating Behavior Questionnaire
    - Babies Basic Needs Questionnaire
    - Infant Feeding Practices
- You will complete your diary cards for the 3 days following the visit
- You will complete your diary cards each day for the 3 days prior to the next study visit

For the intervention group only:

- Study coordinators will provide you with a range of formula volume to be consumed
- You will be given instruction to prepare the formula volume in each bottle on the lower end of what you anticipate the infant will eat.
- You will be provided with handouts on hunger/satiety cues and calming a fussy baby
- You will be given a copy of a Bottle Feeding Basics video, "Happiest Baby on the Block", and a video demonstrating responsive bottle feeding

Visit 3: 2 Month Visit (42-77 days)

- Your child's weight and length will be obtained and recorded for the research.
- You will complete your diary cards for the 3 days following the visit
- You will complete your diary cards each day for the 3 days prior to the next study visit

For the intervention group only:

- You will be given recommended formula volumes for the next month based on Visit 2 procedures

Visit 4: 3 Month Visit (78-109 days)

For the intervention group only:

- Your child's weight and length will be obtained and recorded for the research.
- You will complete your diary cards for the 3 days following the visit
- You will complete your diary cards each day for the 3 days prior to the next study visit
- You will be given recommended formula volumes for the next month based on Visit 2 and 3 procedures

Visit 5: 4 Month Visit (110-140 days)

- Your child's weight and length will be obtained and recorded for the research.
- You will complete your diary cards for the 3 days following the visit
- You will complete your diary cards each day for the 3 days prior to the next study visit

For the intervention group only:

- You will be given recommended formula volumes for the next month based on Visit 2 and 3 procedures
- You will be provided with handouts on soothing fussy infants and feeding recommendations

Visit 6: 5 Month Visit (141-171 days)
For the intervention group only:

- Your child's weight and length will be obtained and recorded for the research.
- You will complete your diary cards for the 3 days following the visit
- You will complete your diary cards each day for the 3 days prior to the next study visit
- You will be given recommended formula volumes for the next month based on Visit 2 and 3 procedures

Visit 7: 6 Month Visit (172-210 days)

- Your child's weight and length will be obtained and recorded for the research.
- You will be asked some survey questions;
    - Baby Eating Behavior Questionnaire
    - Infant Feeding Styles Questionnaire
    - Baby's Basic Needs Questionnaire
    - Infant Feeding Practices

What are my responsibilities if I take part in this research?
If you take part in this research, your major responsibilities will include: Participating infants in the intervention group will be seen monthly until age 6 months where they will be weighed and measured, and parents will complete surveys related to volume of formula consumed, infant appetite, parent feeding style, and infant temperament. Control infants will follow the same procedures, but will not have scheduled visits at ages 3 and 5 months. Instead their visits will correspond to well child clinic visits at ages 1, 2, 4, and 6 months. Most study visits, with the exception of Visits 4 and 6, will occur in conjunction with regular well child care, adding ~15 minutes to each visit.

3. What are the risks and possible discomforts from being in this research study?
Loss of Confidentiality: There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained as required by applicable law and to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

Growth Faltering: There is an unlikely risk that a reduction in formula intake could lead to temporary growth faltering (i.e. failure-to-thrive), though this would be self-limited and could be addressed by subsequently increasing formula intake.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to me?
There is no guarantee that you will benefit from this research. The possible benefits you may experience from this research study include the improvement of infant growth trajectories, reduction of rapid infant weight gain, and reduction in the likelihood of overweight during infancy and beyond for participants.

4b. What are the possible benefits to others?
Medical science may gain further understanding of formula feeding guidelines for infants at risk of becoming overweight.

5. What other options are available instead of being in this research study?
You may choose not to be in this research study.

6. How long will I take part in this research study?
If you agree to take part, it will take you about 6 months to complete this research study. For the intervention group, you will be asked to visit the research site 2 times.

7. How will you protect my privacy and confidentiality if I decide to take part in this research study?

7a. What happens to the information collected for the research?
Efforts will be made to limit the use and sharing of your personal research information to people who have a need to review this information. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed, and there may be situations where disclosure is required by law.

In our research files at Penn State Health (PSH) and Penn State College of Medicine (PSU) we will include these identifiers: you and your child's name/initials, street address, telephone number, date of birth, medical record number, electronic mailing address, and a code.

- A list that matches your name with your code number will be kept in a locked file in the Pediatric Research Recourse Office
- Your research records will be labeled with a code number and your initials and will be kept in a safe area in the Pediatric Research Resource Office
- A copy of this signed consent form will be included in your PSH medical record. This means that other PSH healthcare providers will know you are in this study.

For research records sent to UCLA, you will be identified by a study code number and all elements of dates.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot disclose information that identifies you to anyone not connected with the research. This protection also prevents this information from being used or disclosed for legal proceedings, such as being accessed through a court order. The Certificate of Confidentiality however does not prevent disclosures required by law, such as information about child abuse or neglect and harm to yourself or others. Also, your information may be disclosed in accordance with any consent you provide, including for your medical treatment or use in other research.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

7b. What will happen to my research information and/or samples after the study is completed?
We may use your research information in future studies or may share your information with other investigators for future research without your additional informed consent. Before we use or share your information or samples we will remove any information that shows your identity.

7c. How will my identifiable health information be used?

Instructions: Include the following information in this section:

- Section 7c is mandatory if the research creates, obtains, uses, and/or discloses **protected health information** (PHI) about the research subjects.

- Do **not** include any part of Section 7c unless the research fits the above criteria.
- If the research involves prisoners, add the following statement: "If you are a prisoner, your medical records may also be given to officials and agencies within the criminal justice system when necessary and permitted by law."
- If applicable, describe any limitations on confidentiality based on possible legal issues. For example, if the research team is likely to uncover abuse, neglect, or reportable diseases, explain that this information may be disclosed to appropriate authorities. For example, "As with information contained in research records generally, we will use and disclose your identifiable health information when we are required to do so by law, such as for laws that require us to report child abuse or abuse of elderly or disabled adults. Additionally, unless this study is covered by a Certificate of Confidentiality, we will also comply with legal request or orders that require us to disclose your identifiable health information."

If you give your consent, health information that can be traced to you will be collected for this research study. In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so. We will use and disclose your information only as described in this form and in the PSH Privacy Notice.

The research team may use the following health information:

- Past, present, and future medical records, including identifiable information
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The following people/groups may see, use, and share your identifiable health information:

- PSH/PSU research staff involved in this study
- The PSH/PSU Institutional Review Board (IRB), a group of people who review the research study to protect subjects' rights and welfare
- The PSH/PSU Human Research Protection Program (HRPP)
- The PSH/PSU Research Quality Assurance Office
- Non-research staff within PSH/PSU who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- Federal and state agencies (such as the U.S. Food and Drug Administration, the Office for Human Research Protections, the Department of Health and Human Services, the National Institutes of Health, and other U.S. or foreign government bodies that oversee or review research)
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Organizations that provide independent accreditation and oversight of hospitals and research
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- The sponsor(s) of this study, monitors and auditors, and other people or groups it hires to help perform this research
- Other researchers and medical centers outside of PSU and Penn State Health that are part of this study and their IRBs
- Researchers from other campuses of Penn State University who are part of this study
- A group that oversees the data (study information) and safety of this research

These groups may also review and/or copy your original PSH/PSU records while looking at the results of the research study. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy.

{Add the following paragraph for investigator-initiated research studies if applicable.}
Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your identifiable health information and samples may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

We may remove identifying information from your protected health information. Once we do this, the remaining information will not be subject to the privacy laws. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Because research is an ongoing process, your permission for the use, storage and sharing of your health information will continue indefinitely.

Your privacy rights:

- You have the right to refuse to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you will not be able to take part in this research study.
- You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing using the address on the front of this form. Once permission is withdrawn, you cannot continue to take part in the study.
- If you withdraw your permission, we will stop collecting health information about you for this study; we may continue to use and share your health information that we already have if it is necessary for safety and scientific soundness of the research study; and we will not be able to take back information that has already been used or shared with others.
- You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. However, you may not be allowed to see or copy certain health information that is a part of this research study. This is only for the period of the study. You will be allowed to see that information when the entire research study is complete.

8. What are the costs of taking part in this research study?

8a. What will I have to pay for if I take part in this research study?

For costs of tests and procedures that are only being done for the research study:

- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care (what is normally done) for your condition.
- Examples of research-related tests and procedures that may be provided at no cost to you may include: visits to the study site, procedures, and/or questionnaires. Talk to the study team about which items and procedures this includes.

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research.

- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.
- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies may not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

8b. What happens if I am injured as a result of taking part in this research study?
It is possible that you could develop complications or injuries as a result of being in this research study. If you experience a side effect or injury and emergency medical treatment is required, seek treatment immediately at any medical facility. If you experience a side effect or injury and you believe that emergency treatment is not necessary, you should contact the principal investigator listed on the first page of this consent form as soon as possible and the principal investigator will arrange for medical treatment. You should also let any health care provider who treats you know that you are in a research study.

<u>PSH/PSU compensation for injury</u>

- There are no plans for PSH/PSU to provide financial compensation or free medical treatment for research-related injury.
- If an injury occurs, medical treatment is available at the usual charge.
- Costs will be charged to your insurance carrier or to you.
- Some insurance companies may not cover costs associated with research injuries.
- If these costs are not covered by your insurance, they will be your responsibility.

When you sign this form you are not giving up any legal right to seek compensation for injury.

9. Will I be paid to take part in this research study?
You will receive $50 for each study visit completed for your participation in this research study for a total of $250-$300 depending on which study group you are assigned to (control vs. intervention). If you do not complete the study for any reason, you will be paid for the visits you have completed. The payment will be provided by Greenphire Clincard.

This reimbursement will be issued by an external company called Greenphire, which will issue your reimbursement. You will be issued a ClinCard, which is a debit card that your funds are loaded onto and can be used at your discretion. The research team will give Greenphire some personal information about you, as described below. Greenphire will only use your personal information to process this reimbursement and will not share it with anyone for any other purpose. Details of the debit card system are explained on an additional sheet. If you lose the card, you may be responsible for the replacement fee.

When a visit is completed, funds will be approved and loaded onto your card. The funds will be available within 2-3 business days. In order to assign a ClinCard to you and load funds onto

the ClinCard, Greenphire will need your Study/Subject ID, Name, Address, Social Security Number, and date of birth.

You will have the option to receive updates related to payment alerts via text message and/or email message. Standard text messaging rates will apply. In order to send you messages Greenphire will need your Mobile Phone Number and/or E-mail Address.

Payment received as compensation for participation in research is considered taxable income. If payments from Greenphire exceed $600 in any one calendar year, you will be required to provide your social security number so that Greenphire can file a 1099 (Miscellaneous Income) form on behalf of Penn State. Payment totals are calculated across all research participation at Penn State if you participate in multiple studies.

10. Who is paying for this research study?

Instructions: Include the following information in this section:
- Funding disclosure: Disclose what grantors, institution(s) (e.g., NIH) or companies are involved in the research through funding or grants. If none, say so.
- Conflict of Interest: Include information about any consultative relationships with the sponsor or financial or business interests the investigators may have related to this research.

The institution and investigators are receiving a grant from The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the University of California at Los Angeles (UCLA) to support this research.

The sponsors, NICHD and UCLA are paying PSH/PSU for the research to be done.

11. What are my rights if I take part in this research study?

Taking part in this research study is voluntary.
- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

You may withdraw your participation from this study at any time. We will collect and use all of the data collected up to the point of withdrawn participation.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If I have questions or concerns about this research study, whom should I call?

Please call the head of the research study Dr. Ian Paul, at (717) 531-5656 or the Pediatric doctor on 24-hour call at (717) 531-8521 if you:
- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the research protection advocate in the PSU Human Research Protection Program (HRPP) at (814) 865-1775 if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns, complaints or general questions about the research.
- Have questions about your privacy and the use of your personal health information.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

You may visit the Penn State College of Medicine's Clinical Research web site at http://med.psu.edu/clinical-research/faqs for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and
- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HRPP at (814) 865-1775.

A description of this clinical trial will be available on https://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative, provided the subject or subject representative an opportunity to discuss and consider whether or not to participate in the research, and have answered any questions about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent and Authorization

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and authorize your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name

Signature of Parent(s)/Guardian for Child

By signing this consent form, you indicate that you permit your child to be in this research and authorize your child's information to be used and shared as described above.

_____
Printed name of child

_____	_____	_____	_____
Signature of Parent/Guardian	Date	Time	Printed Name

☐ Parent

☐ Individual legally authorized to consent to the child's general medical care. (See note below.)

Note: Investigators are to ensure that individuals who are not parents can demonstrate their legal authority to consent to the child's general medical care. Contact legal counsel if any questions arise.