HIC 2000028252

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: A randomized control trial to determine weight gain benefits of caloric supplementation for infants with NAS

Principal Investigator: Matthew Grossman, MD

Version Date: September 6, 2021

(*If applicable***) Clinicaltrials.gov Registration #:** NCT04419857

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type “Not Applicable” underneath. 3. Once completed, upload your protocol in the “Basic Information” screen in IRES IRB system.

APPROVED BY THE YALE UNIVERSITY IRB 9/8/2021

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Aim. To determine how early introduction of increased caloric density of feeds relates to the weight trajectory of infants with Neonatal Abstinence Syndrome (NAS).

Hypothesis. We hypothesize that among infants with NAS, introduction of increased caloric density formula or breastmilk within the first 48 hours of birth decreases maximal percent weight loss within the first fourteen days of life compared to normal caloric density formula or breastmilk.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

October 2020-December 2024 Participant Recruitment and Intervention
October 2020-December 2025 Growth Chart Review

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

B. Background and Significance

B1. Incidence of NAS is dramatically increasing leading to increasing costs in the care of children. Neonatal abstinence syndrome (NAS) is a collection of withdrawal signs that occur in newborns whose mothers were taking opioids while pregnant.[1-6] The incidence of NAS has increased substantially during the past two decades.[7,8] NAS cases covered by Medicaid increased by fivefold from 2004 to 2014 and resulted in $462 million in Medicaid costs in 2014.[9]

B2. Infants with NAS are more likely to experience greater weight loss early in the newborn period than in otherwise healthy infants. Infants with NAS will often have high caloric expenditure related to specific withdrawal signs including high muscle tone, jitteriness, sweating, excessive crying, vomiting, and diarrhea.[10] Infants with NAS are also at risk for feeding difficulties which often stems from weak and uncoordinated suckling.[11] The combination of high caloric expenditure and poor feeding can lead to early increased weight loss in the newborn period compared to otherwise healthy infants.[12-14]

B3. Early increased weight loss can lead to increased healthcare utilization. Early increased weight loss is an important indicator of infant health. In otherwise healthy infants, it has been shown to lead to early health care utilization, hypernatremia, and hyperbilirubinemia and dehydration, the two most common causes of neonatal morbidity.[15-18] It has also been shown to lead to decreased breastfeeding rates.[19] In NAS infants, early increased weight loss can trigger an evaluation for failure to thrive.[20,21]

B4. Feeding practices for infants with NAS vary widely across the United States. Though weight loss is widely recognized as a risk in infants with NAS, there are no standard interventions specifically directed at this issue.[2] Feeding practices, including formula type, timing of introduction of high calorie formula, and breastfeeding policies for infants with NAS vary greatly across the United States.[22] Some hospitals introduce high-calorie formula to opioid-exposed infants preventively whereas others wait and start only after infants demonstrate increased or persistent weight loss.[22] This variation exists within hospitals such as YNHH, where currently some

infants will receive preventive high-calorie formula and some will only start to receive it after infants demonstrate increased weight loss at the discretion of the healthcare provider.

B5. Optimal feeding methods to prevent increased weight loss are currently unknown. It has been hypothesized that early caloric enhancement for infants who are exposed to intrauterine opioids can result in improved weight management as it is readily available, easy to implement, and conceptually appealing.[13] One recent study demonstrated the feasibility of preventive introduction of high calorie formula in infants with NAS.[23] However, this preliminary study was conducted in infants with NAS managed via the modified Finnegan scoring method, and was not powered to demonstrate a statistically significant difference on outcomes.[23] Importantly, the effectiveness of high calorie formula in preventing early increased weight loss in NAS infants has not yet been shown.

4. **B6. First-line non-pharmacologic interventions have been shown to demonstrate effectiveness in NAS infant care.** While using pharmacologic interventions to reduce withdrawal symptoms in NAS infants has been the standard of care, newer approaches such as the Eat, Sleep, Console (ESC) method as developed by PI Grossman demonstrate the effectiveness of non-pharmacologic interventions in reducing adverse events and average length of stay for NAS infants.[24,25] The ESC approach for the management of infants with NAS focuses on non-pharmacologic therapies coupled with empowering message to parents, administration of morphine on an as-needed basis, and bypassing the NICU with transfer of infants directly to the inpatient unit. This novel approach led to substantial and sustained decreases in the average length of stay, the proportion of infants treated with morphine, and average hospital costs with no adverse events.[25] The ESC approach is currently the standard of care for infants with NAS at YNHH and at a growing number of hospitals nationwide.[5,6,26-29]

B7. The proposed research can provide insight into optimal feeding methods for infants with NAS. It has the potential to establish best feeding practices in infants with NAS, which currently vary widely within hospitals and across the United States.[22] If increased caloric density feeds are determined to be effective in preventing early increased weight loss, this would lead to significant practice changes for infants with NAS.

B8. Conclusions. The proposed research addresses weight loss in infants with NAS, which is a significant pediatric problem. Studies of cost-effective and easily implementable methods of weight loss prevention in these neonates can help guide management of feeding and postnatal growth in this vulnerable population.

C. PRELIMINARY STUDIES.

C1. Infants with NAS managed via the ESC approach lose increased weight compared to otherwise healthy infants. PI Grossman and Co-I Cheng and Shabanova conducted a retrospective analysis of daily weights in NAS infants and created early weight loss nomograms for both formula-fed and breast-fed infants with NAS. Compared to weight loss patterns of otherwise healthy infants, infants with NAS have substantially greater weight loss and continue to lose weight for longer periods of time (Cheng et al, manuscript in progress, 2020). In this study, overall 27.9% of infants with NAS lost more than 10% of their birth weight, which is a greater percentage than that in the general population[30,31] and can often trigger an evaluation for failure to thrive.[20,21]

C2. Increased caloric density of feeds in infants with NAS is feasible. One recent study demonstrated the feasibility of preventive introduction of high calorie formula in an effort to achieve larger daily weight gains and earlier return to birth weight. However, this preliminary study was conducted in infants with NAS managed via the modified Finnegan scoring method, and was not powered to demonstrate a statistically significant difference on outcomes.[23] PI Grossman and Co-I Cheng and Shabanova conducted a retrospective

analysis of feeding methods and weight loss in 330 NAS infants managed at YNHH. Of infants in the cohort, 130 (39.4%) received increased caloric density of feeds, with 20 (6.1% of total) infants started on Day 0 or 1. 110 (33.3% of total) infants started on day 2 or later. Maximum weight loss happened earlier, though not significantly different, in infants who received increased caloric density feeds starting on day 0 or 1 (mean = 3.3 days) compared to those who started on day 2 or later (mean = 3.7 days). Mean LOS was significantly shorter (5.3 days) in infants who began receiving increased caloric density of feeds on day 0 or 1 compared with infants with a later start date (mean = 6.5 days, p = 0.03). Overall this study demonstrated that those infants who were started on increased caloric density on day 0-1 of life (prior to significant weight loss being recorded) lost less weight, had a shorter length of stay, and reached a weight nadir earlier than those who had received increased caloric density of feeds on day 2 or greater of life (Cheng et al, manuscript in progress, 2020).

C3. Summary. These studies demonstrate the ability of the investigative team to carry out the proposed research. We demonstrated that NAS infants are at risk for early increased weight loss which may lead to a failure to thrive evaluation, and our study as well as others have shown that increased caloric density feeds in infants with NAS is feasible and safe.

4. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

D. RESEARCH PLAN.

D1. Aim. To determine how early introduction of increased caloric density of feeds relates to the weight trajectory of infants with NAS

D2. Hypothesis, Rationale, and Study Design. We hypothesize that among infants with NAS, introduction of increased caloric density formula or breastmilk within the first 48 hours of birth decreases maximal percent weight loss within the first fourteen days of life compared to normal caloric density formula or breastmilk. **Early introduction of increased caloric density feeds should provide the highest likelihood of preventing increased weight loss as compared to normal infants.** In a **phase 2, double-arm trial**, we will stratify infants based three criteria: (1) mother's feeding preference (exclusive formula vs. any breastmilk), (2) gestational age at birth (36-37 weeks vs. $\geq$ 38 weeks), and (3) infant sex (male vs. female), and randomize infants to normal caloric density of feeds (20 kcal/oz) or increased caloric density of feeds (24 kcal/oz). Breastmilk is approximately 20 kcal/oz, although there can be some variation in caloric density among women during the postpartum period. This study will use formula powder to enrich the pumped breastmilk in the high caloric-density diet group by 4 kcal/oz to achieve a caloric density of approximately 24 kcal/oz. The trial will be monitored for safety.

D3. Eligibility Criteria. We will enroll mothers and infants over approximately a 17-month period. Mothers will be included based on 1) receiving methadone/buprenorphine during pregnancy 2) age 18-45 at time of delivery and excluded if 1) not retaining custody of infant after delivery. Infants will be included based on 1) delivery at YNHH hospital 2) born to mothers aged 18-45, 3) exposure to methadone or buprenorphine in utero and excluded based on 1) <36 weeks gestation, 2) >48 hours in NICU, 3) Major congenital malformation, as defined by the CT Department of Public Health's Birth Defects Registry 4) Weight <2200g 5) Withdrawn by mother before randomization. Participants will only join the study as a mother/infant dyad, if one is excluded from the study then both are excluded.

D4. Study Procedures.

D4.1. During Hospitalization. The mother's preference for feeding – either exclusively formula (Figure 1, Strata 1) or any breastmilk (Figure 1, Strata 2) - will be determined. Based on the mother's feeding preference, the gestational age, and the infant sex, the infant will be randomized within the first 48 hours after delivery to normal caloric density of feeds (20 kcal/oz) or increased caloric density of feeds (24 kcal/oz) (Figure 1).

If the mother plans to exclusively formula feed (Figure 1, Strata 1), the trial will be double-blinded. Infants will be randomized, nursing staff will be notified to draw from bin A or B, containing pre-mixed formula of either 20 kcal/oz (Figure 1, Strata 1, Arm A) or 24 kcal/oz (Figure 1, Strata 1, Arm B) with hidden labels. The infant will be fed on-demand.

If the mother plans to breastfeed (Figure 1, Strata 2), the trial will be partially blinded. **If the infant is randomized to the normal caloric density (20 kcal/oz) arm**, mothers will breastfeed and/or pump on demand. If she chooses during the course of the hospitalization to supplement feedings with formula, the infant will receive 20kcal/oz formula (Figure 1, Strata 2, Arm C), and nurses will draw from bin C containing pre-mixed formula of 20 kcal/oz (Figure 1, Strata 2, Arm C) with hidden labels. **If the infant is randomized to the increased caloric density (24 kcal/oz) arm** (Figure 1, Strata 2, Arm D), mothers will breastfeed on demand and/or pump breastmilk that will not be enriched. If the mother chooses during the course of the hospitalization to supplement feedings with formula, the infant will receive 24 kcal/oz formula (Figure 1, Strata 2, Arm D). Nurses will draw the formula from bin D containing pre-mixed formula of 24 kcal/oz with hidden labels. Nurses will be blinded to which bin contains 20 or 24 kcal/oz formula.

All feedings will be on demand, but are recommended to be 1-2 oz every 2-3 hours (or 8-12 breastfeeding per day) – currently standard of care in the nursery. All feedings – including type, amount, and instances of breastfeeding – and all stools will be recorded by nursing. Infant weights will be assessed twice daily. If the two daily weights differ by more than 10g, nurses will weigh the infant a third time, and the two closest weights will be averaged to determine that day's weight.

Currently, the standard of care of infants in the hospital who are getting an increased caloric diet due to NAS are not routinely screened for clinical markers. As this is the current standard of care, infants receiving an increased caloric diet are will not be screened with additional blood tests.

D4.2. Upon Hospital Discharge. Upon discharge, on average 6 days, nursing will review with the mother instructions for formula preparation and/or breastmilk enrichment depending on strata and randomization arm (see Section II.B.4. for instructions on storage, preparation, and use). Mothers of infants randomized to Strata 2, Arm C will be given separate discharge instructions; they will be sent home with a two-week supply of Similac formula to use to prepare formula or to use to enrich pumped breastmilk. For the "any breastfeeding" arm, there is a standard-calorie (Arm C) and high-calorie group (Arm D). The standard-calorie group (Arm C) will receive either breastmilk (from the nipple or pumped) or 20 kcal formula. Breastmilk is considered to be approximately 20 kcal without any supplementation, thus no formula will be added to the breast milk in the standard-calorie group. The high-calorie group (Arm D) will receive either breastmilk (from the nipple or pumped) or 24 kcal formula. Because breastmilk on its own is approximately 20 kcal, mothers in this group will enrich pumped breastmilk with 4 kcal of formula to achieve a total caloric density of 24 kcal. The mothers will not be told the calorie content of the two-week formula supply or enrichment powder.

There is potential for unblinding of nurses of patients who are in groups C or D upon discharge education because different instructions will be given within Arms C and D of Strata 2. Mothers will be blinded while in the hospital and will not be told which group their infant was in until the conclusion of the 14-day study period. At discharge, mothers will be provided with loaner scales and a feeding log to record all feedings, including type, amount, and instances and length of time of breastfeeding, as well as instances of stools. They will be instructed to feed their infants on demand, but are recommended to be 1-2 oz every 2-3 hours (or 8-12 breastfeeding per day) – currently standard discharge instructions from the nursery. They will also be taught to record infant weights twice daily. At this time, nurses will confirm that mothers agree to be called daily by study staff to obtain recorded feeding, stool, and weight information.

D4.3. Post-Hospitalization. Infants will continue on the assigned feeding and twice-daily weights until **14 days of life.** Mothers or other caregivers will record feedings [time, method (formula, breastfed, pumped), ounces or length of time if breastfeeding], instances of bowel movements, and daily weights twelve hours apart. Study personnel will call mothers daily to obtain recorded feeding, stool, and weight information. If the mother does not answer the call the study team will follow up with a text message. Text messaging may also be used to send pictures of the daily log information. Following 14 days, infant diet should be determined by infant's pediatrician. The study team will inform the mother which group she was in at this point so that she can have a well-informed discussion with the pediatrician. Mothers will no longer be asked to take daily weights or record feedings or bowel movements. As is standard of care for all infants, infants should be seen for their two-week well child visit and this will mark the transition to tracking weights recorded by the child's pediatrician.

Assigned feeding will stop earlier if 1) the infant loses > 12% of his or her birth weight, 2) is still losing weight at the 10-day-old time-point, 3) or is gaining an average of >75g per day at the 10-day-old time-point. If assigned feeding is stopped during hospitalization, the attending pediatric hospitalist will be notified and feedings will be at the hospitalist's discretion. If the assigned feeding is stopped post-hospitalization, the infant's pediatrician will be notified and feedings will be at the pediatrician's discretion. The rest of the management of the infant will be based on usual care which includes the standard ESC approach. Infant weights and lengths will also be obtained from the pediatrician's office at regularly scheduled well child checks until the first year of life (at 1, 2, 4, 6, 9, and 12 months). In the rare case that an infant has not regained birth weight by 14 days and does not have a 2-week well child check scheduled at or prior to 14 days, the pediatrician will be informed and feeding will be at the pediatrician's discretion. In these cases where the study feedings are stopped, the infants will be withdrawn from the study and no further data will be collected. The scale will need to be returned, and the pediatrician will be informed. All clinical care and feedings will be at the pediatrician's discretion following withdrawal from the study.

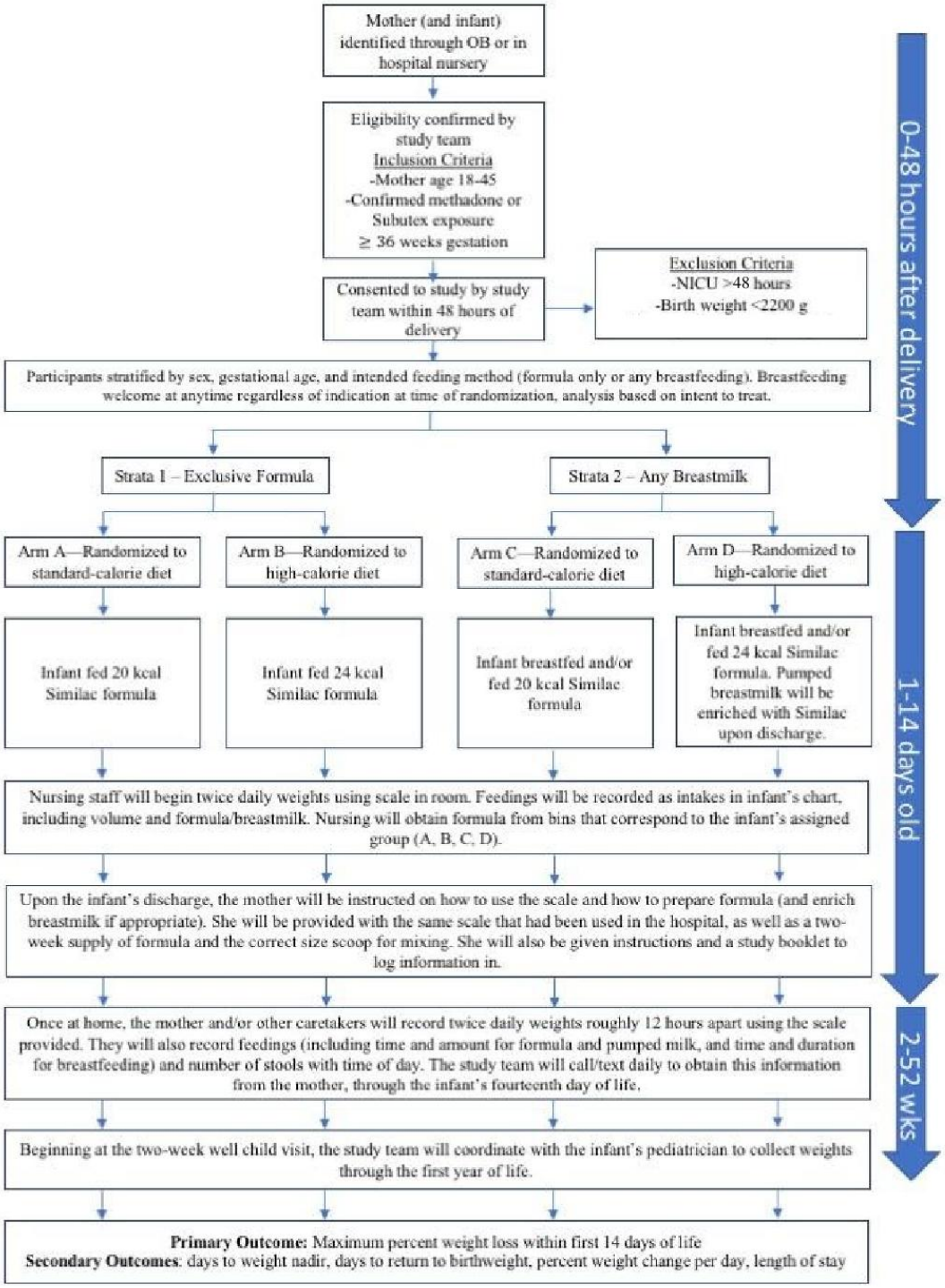
D5. Outcome Measures. The **primary outcome is maximal percent weight loss within the first fourteen days of life,** defined as the maximum percent weight loss of the infant achieved within the first fourteen days of life compared to birth weight. Weight loss will be calculated from the average of twice daily weights that are obtained by nursing during hospitalization or by the mother and/or other caregivers post-hospitalization, and compared to birth weight. If the two daily weights differ by more than 10g, nurses will weigh the infant a third time, and the two closest weights will be averaged to determine that day's weight.

Secondary outcomes include days to maximal percent weight loss, days to return to birthweight, percent weight change per day, and length of stay. Days to maximal percent weight loss will be calculated by determining the day of life on which maximum percent weight loss was achieved when compared to birth weight. Days to return to birthweight will be calculated by determining the day of life that the infant either regained birthweight within the first 14 days or surpassed birthweight. In the rare case that an infant has not

regained birth weight by 14 days and does not have a 2-week well child check scheduled at or prior to 14 days, the pediatrician will be informed and feeding will be at the pediatrician's discretion. The pediatrician's office will be called at the 1 month well child check and will be asked when the infant regained birth weight to determine days to return to birthweight. Percent weight change per day will be calculated by subtracting the first weight obtained each day from the first weight obtained the day prior and calculating the percent weight change based on the weight obtained the day prior. The length of stay will be calculated by determining the number of days of hospitalization for the infant.

Figure 1. Study flow diagram

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Mother (and infant) identified through OB or in hospital nursery
Eligibility confirmed by study team
Inclusion Criteria
-Mother age 18-45
-Confirmed methadone or Subutex exposure
≥ 36 weeks gestation
Consented to study by study team within 48 hours of delivery
Exclusion Criteria
-NICU >48 hours
-Birth weight <2200 g
Participants stratified by sex, gestational age, and intended feeding method (formula only or any breastfeeding). Breastfeeding welcome at anytime regardless of indication at time of randomization, analysis based on intent to treat.
Strata 1 – Exclusive Formula
Strata 2 – Any Breastmilk
Arm A—Randomized to standard-calorie diet
Arm B—Randomized to high-calorie diet
Arm C—Randomized to standard-calorie diet
Arm D—Randomized to high-calorie diet
Infant fed 20 kcal Similac formula
Infant fed 24 kcal Similac formula
Infant breastfed and/or fed 20 kcal Similac formula
Infant breastfed and/or fed 24 kcal Similac formula. Pumped breastmilk will be enriched with Similac upon discharge.
Nursing staff will begin twice daily weights using scale in room. Feedings will be recorded as intakes in infant's chart, including volume and formula/breastmilk. Nursing will obtain formula from bins that correspond to the infant's assigned group (A, B, C, D).
Upon the infant's discharge, the mother will be instructed on how to use the scale and how to prepare formula (and enrich breastmilk if appropriate). She will be provided with the same scale that had been used in the hospital, as well as a two-week supply of formula and the correct size scoop for mixing. She will also be given instructions and a study booklet to log information in.
Once at home, the mother and/or other caretakers will record twice daily weights roughly 12 hours apart using the scale provided. They will also record feedings (including time and amount for formula and pumped milk, and time and duration for breastfeeding) and number of stools with time of day. The study team will call/text daily to obtain this information from the mother, through the infant's fourteenth day of life.
Beginning at the two-week well child visit, the study team will coordinate with the infant's pediatrician to collect weights through the first year of life.
Primary Outcome: Maximum percent weight loss within first 14 days of life
Secondary Outcomes: days to weight nadir, days to return to birthweight, percent weight change per day, length of stay
0-48 hours after delivery
1-14 days old
2-52 wks

5. **Genetic Testing** **N/A ☒**
6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Infants with NAS born to mothers aged 18-45 with methadone or buprenorphine exposure during pregnancy.

7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☒Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☒Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

This study includes infants with in-utero methadone or buprenorphine exposure in order to improve their risk for early increased weight loss. Mothers on methadone or buprenorphine will be consented and infants will begin the study within 48 hours after delivery.

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?
   Inclusion criteria are:
   Mothers:
   - Inclusion Criteria:
     - Receiving methadone or buprenorphine (Subutex or Suboxone)
     - Age 18-45 at time of delivery
   - Exclusion Criteria:
     - Not retaining custody of infant after delivery

   Infants:
   - Inclusion Criteria:
     a. Delivered at YNHH hospital,
     b. Born to mothers aged 18-45,
     c. Exposed to methadone or buprenorphine in utero
   - Exclusion Criteria:
     a. <36 weeks gestation,
     b. >48 hours in NICU,
     c. Major congenital malformation, as defined by the CT Department of Public Health's Birth Defects Registry (https://portal.ct.gov/DPH/Family-Health/Birth-Defects-Registry/Connecticut-Birth-Defects-Registry)
     d. Weighs <2200g
     e. Withdrawn by mother before randomization

Participants will only join the study as a mother/infant dyad, if one is excluded from the study then both are excluded.

9. How will **eligibility** be determined, and by whom?

Obstetricians, pediatric hospitalists, and study staff will determine eligibility.

If the subject is recruited prenatally, study staff will set up a phone or zoom appointment with pregnant women (age 18-45) on methadone or buprenorphine at any point in pregnancy, to determine and record study eligibility information and consent the participant. During these appointments, study staff will

(1) discuss study inclusion/exclusion criteria (see above)
(2) confirm methadone/buprenorphine treatment is received from a licensed treatment program
(3) confirm that mothers are planning to deliver their infant(s) at Yale New Haven Hospital
(4) confirm that mothers do not intend to place the infant(s) for adoption
(5) confirm mother's willingness to participate in the study (including attending regularly-scheduled well-child visits through the first year of life to get follow up weights with pediatrician)
(6) Consent forms will be signed and scanned into the mother's chart.

Daily, study staff will conduct a chart review to identify women admitted to the postpartum unit with methadone or buprenorphine in utero exposure and/or women with an infant showing a diagnosis code for NAS. Once women have been identified through chart review and pediatric hospitalists gauge interest in participating in the study, a member of the study team will call into the mother's room within 48 hours of delivery to determine study eligibility. Study staff will confirm eligibility through chart review and/or over phone with the mother. A consent form will be signed by mother and appropriate study staff/PI and mother will be provided with a signed copy, scanned into mother's and infant's Epic chart and the signed copy will be returned to the mother to keep for her reference. The nurse manager or assigned proxy will verify eligibility of mother and infant before randomizing or submitting randomization request.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Participation in the study involves randomization to a standard-calorie or high-calorie diet. This is a decision often made by the attending physician but will be assigned through randomization in this study. There is not currently a standard of care for caloric-density of feeds for infants with NAS (both 20 kcal/oz and 24 kcal/oz are prescribed) and there is variability at YNHH currently based on the provider's assessment. Mothers will still be able to make independent decisions about breastfeeding throughout the study. Therefore, there is a minimal risk of randomization of feeding rather than having the provider decide on caloric density of feeds. They are the following:

(1) Infants may continue to lose weight by the 10-day timepoint
(2) lose >12% of his or her birth weight at any point after birth
(3) gain an average of >75g per day at the 10-day timepoint

We plan to have safety processes in place as listed below to minimize the risks in Section 11. If any of these risks are met, infants will be immediately withdrawn from the study and feeding will be at the discretion of the attending pediatrician. There will be a twice daily requirement to record infant weight for the first two weeks of life (including at home after hospital discharge), but this will also provide useful information about the infant's growth to both the mother and the caring pediatrician.

11. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.
If infants are still losing weight at 10 days or lose >12% of their body weight assigned feeding will be stopped and feeding will be at the discretion of the pediatric hospitalist if the patient is still hospitalized, or at the discretion of the primary pediatrician if the patient is no longer hospitalized. If infants are gaining an average of >75g per day at 10 days, they will be taken off the assigned feeding and feeding will be at the discretion of the pediatric hospitalist if the patient is still hospitalized, or at the discretion of the primary pediatrician if the patient is no longer hospitalized. If the diet is changed, the infant will be withdrawn from the study and no further data will be collected on that infant.

12. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? Greater than minimal risk
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

Authority for monitoring data and safety will reside with the principal investigator who will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

We will have an **independent safety monitor** who has the responsibility of timely ongoing monitoring of reports adverse events and reporting of these events to the principal investigator. The monitor will be a pediatric hospitalist not involved with the trial. The study team will monitor each child daily for pre-defined adverse events, particularly weight loss > 12% of birthweight. The identification of serious adverse events will begin when a member of the team reports an adverse event. The PI or his/her designee will conduct a prompt investigation and will inform the monitor of the event as soon as possible. The monitor will then conduct additional investigations, as needed, prior to reporting to the principal investigator and IRB.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. **We do not view the risks associated with the inclusion of children and pregnant women as minimal risks.**

2. Given the now established safety and validity of the current **use of standard calorie formula and increased caloric density formula/breastmilk in infants**, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Dr. Matthew Grossman according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented***.*** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

x All Co-Investigators listed on the protocol.
□ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
□ National Institutes of Health
□ Food and Drug Administration (Physician-Sponsored IND #_____)
□ Medical Research Foundation (Grant_____)
□ Study Sponsor
X Other: **Independent safety monitor**

The principal investigator Dr. Matthew Grossman and independent study monitor (a pediatric hospitalist not involved in the study) will conduct an independent review of all adverse events upon completion of every study subject. The principal investigator and independent study monitor will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Baseline demographic and clinical characteristics for mothers and infants will be compared using chi-squared test and Fisher exact test for categorical variables and Student's t-tests or Wilcoxon rank sum test for continuous variables. Primary outcome of maximal percent weight loss for infants randomly assigned to standard-calorie versus high-calorie formula will be assessed using the Wilcoxon rank sum test in the unadjusted analysis, and using bootstrapped 95% confidence intervals (95%CIs) for the median maximum weight loss percent obtained from quantile regression modeling for repeated outcomes (daily percent weight loss during first 14 days of life), adjusting for delivery type (cesarean vs. vaginal), feeding type, gestational age at birth and infant's sex. For the unadjusted analyses of the secondary outcomes, we will use Wilcoxon rank sum test to compare the length of stay (LOS), the log-rank statistic for the comparison of time-to-event responses (days to weight nadir and days to return to birth weight), and using the quantile regression for percent weight change per day. We will construct Kaplan-Meier curves for the days to weight nadir and days to return to birth weight. We will plot the median trajectories of change in the percent weight loss since birth across the 14-day follow up period using the quantile regression approach for repeated outcomes, with a spline effect for time (day of life since birth) and 95% CIs obtained from 500 non-parametric bootstrapped samples (2.5^{th} and 97.5^{th} percentiles). Primary analysis will be based on the intent-to-treat approach using the two-group comparison (randomized to standard-calorie versus high-calorie formula), and the secondary analysis will be based on the four-group comparison (always on standard-calorie, always on high-calorie, standard- changed to high-calorie, and high- changed to standard-calorie). Pre-specified randomization-related sub-group analyses will include stratifying the analysis by feeding type (exclusive formula vs. any breastmilk), by gestational age at birth (<38 weeks vs. $\geq$ 38 weeks), and by infant's sex (male vs. female). Another pre-specified subgroup analysis will be based on stratifying by type of delivery (vaginal vs. Cesarean). No interim analyses will be conducted for this study. Statistical significance will be established at the two-sided alpha level of 0.05. Statistical analyses will be implemented in R and SAS 9.4 (Cary, NC) statistical software.

Sample size considerations: There is one primary outcome and four secondary outcomes. Primary outcome is: 1) **maximal percent weight loss**. Secondary outcomes: 1) days to maximal percent weight loss, 2) days to return to birthweight, 3) percent weight change per day, and 4) length of stay. Using the comparison of medians (quantile regression with tau=0.50), with 42 subjects per group, we will have 80% power at the two-sided alpha of 0.05 to detect a minimum difference of 1% in the median maximum percent weight loss between infants in the standard- vs. high-calorie groups. This effect size is reasonable, given that our study based on a retrospective cohort sample with similar characteristics in the same institution revealed an average maximal weight loss of -8.5%, and decreasing it by at least 1% is feasible. Using the log-rank test, with 42 subjects per group, we will have 80% power at the two-sided alpha of 0.05 to detect a minimum difference of 1 day for the median days to weight nadir and for the median days to return to birth weight. Taking into account an anticipated conservative attrition rate of 20%, we will need to recruit and randomize 106 total subjects, with 53 per group: 42/(1-0.2)=53 subjects per group. However, we will randomize 56 per group (for a total N=112), in order to accommodate stratified randomization: maternal feeding preference (any breastfeeding vs. exclusive formula: 60% vs. 40%), infant's sex (Male vs. Female: 50% vs. 50%) and gestational age at birth (36 – 37 weeks vs. > 38 weeks: 20% vs. 80%) and performed using permuted block sizes.

Randomization will be stratified by maternal feeding preference (any breastfeeding, exclusive formula: 60% vs. 40%), infant's sex (Male, Female: 50% vs. 50%) and gestational age at birth (36 – 37 weeks, ≥ 38 weeks: 20% vs. 80%) and performed using varying block sizes.

Additional variables may affect our primary outcome, such as infant starting weight and morphine treatment of withdrawal. However, if the randomization works as intended, these variables will not become confounders in our analysis. This is because we anticipate that our randomization will produce randomized groups that are balanced with respect to each of those variables (ie: infant birth weight and morphine treatment of withdrawal). As our primary goal is not to study the effects of other variables on our outcome of interest (maximal percent weight loss), but rather to study the effect of early introduction of caloric density on the outcome.

If confounding does occur, we plan to resort to an analytical approach to balance the randomized groups and sensitivity analysis if the sample size is small for some of the potential confounders (for example, excluding subjects with a rare confounder from the analytical sample), but this would not be our primary approach to statistical analysis. In addition, if the randomization produces groups that are not balanced with respect to our a priori specified variables (ie gestational age at birth, delivery type, feeding type, and infant's sex), then we will control for these using propensity scores or adjusted models for the outcomes.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒**N/A**

B. DRUGS/BIOLOGICS ☒**N/A**

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*: *Similac infant formulas*

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
2. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☐
3. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

For decades, infant formula feeding has been widely used as an alternative to breastfeeding for preterm and term infants. While human milk is optimal due its nutrient composition, anti-infective properties, and high concentration of maternal antibodies, not all infants are able to consume human milk and not all mothers are able to exclusively breastfeed. Infant formula is often substituted for breastmilk in cases of metabolic intolerance to components of human milk (e.g., lactose) and potential exposure to infectious organisms and/or drugs and medications which can be toxic to the infant (RT Hall et al, Pediatrics Review, June 2000).

Infant formula is most often in the form of a powder which is safely and easily mixed with clean drinking water. Infant formula is enriched with calories and contains all of the major macronutrients found in breastmilk, including but not limited to proteins, fats, carbohydrates. Additionally, it is well-documented that the mineral and vitamin content of standard formula is adequate to meet the nutritional needs of infants. The standard calorie density is 20 kcal/oz and feedings are typically 1-2 ounces given every 2-3 hours (RT Hall et al, Pediatrics Review, June 2000). In the hospital newborn nursery, both 20 kcal/oz and 24 kcal/oz formula are ready-made in 2 oz bottles.

3. **Source:** Identify the source of the drug or biologic to be used.
The hospital's pharmacy will provide the formula.

a) Is the drug provided free of charge to subjects? ☒**YES** ☐**NO**
If yes, by whom? The formula will be purchased by the study team and a 14-day supply will be provided to participants free of charge.

4. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

Similac brand formula will be used throughout the study. Powdered infant formula will be stored in a cool, dry, indoor place. Ready-made formula will be provided in the infant nursery, in either 20 or 24 kcal densities, depending on the randomization of the trial. Upon infant discharge, mothers will be instructed on how to mix formula powder with water to make infant formula. They will be provided scoops in either size A (8 g scoop) or size B (10 g scoop). This will allow them to mix the formula powder with the same 2 oz of water to achieve either 20 (using the 8 g scoop) or 24 kcal (using the 10 g scoop) formula. If a mother is in the high-calorie breastfeeding group and chooses to pump breastmilk, she will be asked upon discharge to add a small scoop (1.6 g scoop provided) of powder formula to enrich the calories of 2 oz of pumped breastmilk to roughly 24 kcal total. Mixed formula and breastmilk should not be left unrefrigerated for more than one hour and partially consumed bottles should be discarded. Feedings are recommended to be 1-2 ounces every 2-3 hours. This is only a recommendation in the study and mothers and/or care providers make the final decision on feeding times and amounts; we just ask that they keep a log of the feedings and report it to the study team.

Check applicable Investigational Drug Service utilized:

☒ **YNHH IDS** ☐ **CMHC Pharmacy** ☐ **West Haven VA**
☐ **PET Center** ☐ **None**
☐ **Other:**

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation*.

4. Use of Placebo: ☒**Not applicable to this research project**

5. **Continuation of Drug Therapy After Study Closure** ☐**Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☒ **Yes** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. Participants are welcome to continue using the commercially available infant formula open-label following the conclusion of the 14-day intervention period. Formula will not be provided by the study team after the 14-day study intervention, but mothers are welcome to continue to purchase the same type of formula after the conclusion of the study. If cost is an issue, programs such as Women, Infants, and Children (WIC) can help to cover the cost if mothers qualify.

☐ **NO** If no, explain why this is acceptable. *Write here*

B. DEVICES ☒**N/A**

Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☐No

***If Yes, please be aware of the following requirements*:**

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: 112 participants (anticipated 60% any breastfeeding and 40% formula only)

b. If this is a multi-site study, give the total number of subjects targeted across all sites: *Write here*

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☒ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

*** Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. Patients will be identified both through OB offices and through chart review in the nursery. The OB offices will identify pregnant women currently on methadone or buprenorphine that might qualify for the study. The study team will screen the electronic inpatient list for the Well Newborn Nursery at each hospital to identify infants that are likely to have NAS based on the mother's medications.

b. Describe how potential subjects are contacted. When the OB office identifies a potential participant, they will ask the patient if they are willing to be contacted by the study team. If they agree, the study team will reach out in person or by phone and inform the mother about the study and what to expect. The consent/permission process for mothers recruited through OB offices will be completed before delivery at an OB visit or in the hospital within 48 hours of delivery. When the study team identifies a potential

participant through chart review, a hospitalist will briefly describe the study and ask them if they are interested. If they are interested, a study team member will call them to go into detail about the study and answer any questions. The mother will then be given a written consent form that she will sign if she agrees to participate. The signed consent form will be scanned into the mother's and infant's charts. Other participants will be first contacted by a hospitalist and then the study team will follow up with them to go over the study and consent/permission form.

c. Who is recruiting potential subjects? Any study team member can recruit potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☒Yes, some of the subjects

☐No

If yes, describe the nature of this relationship.

Dr. Grossman and Dr. Cheng are pediatric hospitalists who may have some patients enrolled in the study as their active patients.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☒ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

In order to recruit patients into the study, we will need to screen each patient's electronic medical records even prior to approaching them for authorization.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

We will need PHI to screen patients prior to approaching them for participation in the study. Therefore, a signed authorization is not possible prior to the use of PHI. No PHI will be disclosed to other parties without written authorization from the patient's parent/guardian.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   A hospitalist will ask eligible women if they are interested in learning more about the study. If they are, a paper consent form will be provided, and a study team member will call into their room to talk more about the study. The study team member will address questions about the study rationale, procedures, risks and benefits. In order to identify and clarify any misconceptions, women will be encouraged to ask questions about the research procedures and their associated risks. If at the end of this she is interested in consenting to the study and providing permission for her infant to participate in the study, then she will be instructed to sign the consent/permission form. This form will then be scanned into both her chart and the infant's chart. Eligibility will be conformed once again by the nurse manager or proxy, and then the participant will be randomized. The randomization request must be sent within 48 hours of delivery. The signed consent/permission form will be returned to the mother for reference.

   Eligible women may also give consent/permission during the prenatal period. Potentially eligible participants will be identified by staff at the OB office and they will share information about the study with the Potential participant. If she is interested in learning more, a study team member will call the patient and go through the study with the potential participant and questions about the study rationale, procedures, risks and benefits. In order to identify and clarify any misconceptions, women will be encouraged to ask questions about the research procedures and their associated risks. If at the end of this she is interested in consenting to the study and providing permission for her infant to participate in the study, then she will be able to sign the written consent form at a subsequent OB visit. This form will then be scanned into her chart. Once on the postpartum floor, it will be verified that she is still interested in participating in the study. The consent/permission form will be added to the infant's chart at this time. Eligibility will be conformed once again by the nurse manager or proxy, and then the randomization request will be sent to the IDS. The randomization request must be sent within 48 hours of delivery. The signed consent/permission form will be returned to the mother for reference.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   All subjects will be neonates and therefore cannot legally consent on their own. Study staff will assess the mother's ability and capacity to consent to the research by asking them to describe the research study in her own words and demonstrate understanding of the theoretical benefits and risks to the infant.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

   All conversations with non-English speaking mothers regarding comprehension for research will be conducted with a certified medical interpreter. Similarly, with the assistance of a certified medical

interpreter, mothers will be asked to phrase the research study in their own words and demonstrate understanding of the theoretical benefits and risk to the infant should they choose to enroll in the study. All written materials will be translated to their preferred language.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☒ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒**Not Requesting any consent waivers:**.

☒**Requesting a waiver of signed consent:** *All procedures prior to signed consent would be minimal risk and do not require a waiver (under revised common rule or FDA regs)*
☒ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*
☐ **Entire Study (**Note that an information sheet may be required.)

☒ **Requesting a waiver of consent:**
☒ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*
☐ **Entire Study**

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? *We will collect baseline data from birth visit of infants with a diagnosis of neonatal abstinence syndrome. We will collect mother and infant demographic data, data related to the*

care of the infant in the hospital, and feeding and weight information during the 14-day study period. All data will be de-identified and compliant with HIPAA.

2. How will the research data be collected, recorded and stored? *Data will be collected over the phone and through Epic, as well as in person. All data will be entered into Excel and stored on a password-protected encrypted laptop in a secure Box.*

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? *All PHI and confidential information will be stored on an encrypted, password-protected laptop in a secure Box.*

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. *All HIPAA identifiers will be deleted upon conclusion of the study.*

6. If appropriate, has a Certificate of Confidentiality been obtained? *With NIH funding, yes.*

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The participants receiving the high-calorie formula intervention may be at a decreased risk of losing >10% of their body weight. For both the intervention and the control groups, mothers will be able to weigh the infant daily to track the infants' growth. We expect that early caloric enhancement for NAS infants results in an earlier weight nadir, lower maximum percent weight loss, and faster return to birth weight than those who are fed standard-calorie formula or breastmilk. It is our hope that the results of the study will help in the standardization of feeding methods and care for NAS infants in a cost-effective, easily implementable manner. Additionally, mothers will have access to scales and daily check-ins by the study team while they are home from the hospital through the first 14 days of life. The study team will alert them of any excessive weight gain or weight loss and direct them to seek medical care if appropriate.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research? *Potential study subjects are not required to participate in the study and will continue to receive standard of standard of care treatment when they opt out.*

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   Mothers who consent to participate will receive a five dollar gift card.
3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   There is no cost to the subject associated with participation in the research. A loaned scale will be provided to them at no cost upon hospital discharge in order to weigh the infant daily at home. Two-week supply of formula will also be provided free of charge.
4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

    a. Will medical treatment be available if research-related injury occurs? *Yes*
    b. Where and from whom may treatment be obtained? *Yale New Haven Hospital*
    c. Are there any limits to the treatment being provided? *No*
    d. Who will pay for this treatment? *The parent(s)/guardian(s) of the infant and/or their insurance provider*
    e. How will the medical treatment be accessed by subjects? *Through the study team*

IMPORTANT REMINDERS

Will this study have a billable service? **Yes** ☐ **No** ☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes** ☐ **No** ☒

If Yes, please answer questions a through c and note instructions below.
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes** ☐ **No** ☐
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes** ☐ **No** ☐
c. Will a novel approach using existing equipment be applied? **Yes** ☐ **No** ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

1. Kocherlakota P. Neonatal Abstinence Syndrome. *PEDIATRICS*. 2014;134(2):e547–e561. doi:10.1542/peds.2013-3524.

2. McQueen K, Murphy-Oikonen J. Neonatal Abstinence Syndrome. Longo DL, ed. *N Engl J Med*. 2016;375(25):2468–2479. doi:10.1056/NEJMra1600879.

3. Wachman EM, Schiff DM, Silverstein M. Neonatal Abstinence Syndrome. *JAMA*. 2018;319(13):1362. doi:10.1001/jama.2018.2640.

4. Grossman M, Berkwitt A. Neonatal abstinence syndrome. *Seminars in Perinatology*. 2019;43(3):173–186. doi:10.1053/j.semperi.2019.01.007.

5. Dodds D, Koch K, Buitrago-Mogollon T, Horstmann S. Successful Implementation of the Eat Sleep Console Model of Care for Infants With NAS in a Community Hospital. *Hospital Pediatrics*. 2019;9(8):632–638. doi:10.1542/hpeds.2019-0086.

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