COVER PAGE

Study Title: Enhanced Early Nutrition for Preterm Infants to Improve Neurodevelopment and Minimize Metabolic Risk

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PROTOCOL TITLE:

Enhanced Early Nutrition for Preterm Infants to Improve Neurodevelopment and Minimize Metabolic Risk

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Table of Contents.

1.0 Objectives 7
2.0 Background 7
3.0 Study Outcomes 11
4.0 Study Intervention 11
5.0 Procedures Involved 12
6.0 Data and Specimen Banking 16
7.0 Sharing of Results with Participants 17
8.0 Study Duration 17
9.0 Study Population 17
10.0 Vulnerable Populations 17
11.0 Local Number of Participants 18
12.0 Local Recruitment Methods 18
13.0 Withdrawal of Participants 19
14.0 Risks to Participants 19
15.0 Potential Benefits to Participants 20
16.0 Data Management 20
17.0 Confidentiality 22
18.0 Provisions to Monitor the Data to Ensure the Safety of Participants 22
19.0 Provisions to Protect the Privacy Interests of Participants 23
20.0 Compensation for Research-Related Injury 24
21.0 Consent Process 24
22.0 Setting 25
23.0 Multi-Site Research 25
24.0 Resources Available 25
25.0 References 25

ABBREVIATIONS/DEFINITIONS

- VLBW: Very Low Birth Weight (weighing <1500 grams at birth)
- NICU: Neonatal Intensive Care Unit
- GA: Gestational Age
- CA: Corrected age for prematurity
- ADP: Air Displacement Plethysmography
- ERP: electrophysiologic
- FFM: Fat-free mass
- FM: Fat mass
- IGF-1: Insulin Like Growth Factor-1
- MRI: Magnetic Resonance Imaging
- MDI: Mental Developmental Index
- IGF-BP3: Insulin Like Growth Factor Binding Protein-3
- GIR: Glucose Infusion Rate
- DOL: Day of Life
- IL: Intralipids
- IV: Intravenous
- TPN: Total Parenteral Nutrition
- MMN: Mismatch Negativity
- VEP: Visual Evoked Potentials
- CNBD: Center for Neurobehavioral Development
- SNAP: Score for Neonatal Acute Physiology
- EMR: Electronic Medical Record
- ROP: Retinopathy of Prematurity
- NEC: Necrotizing Entercolitis
- CTSI: Clinical and Translational Science Institute
- DSMC: Data Safety and Monitoring Committee

STUDY SUMMARY

Study Title	Enhanced Early Nutrition for Preterm Infants to Improve Neurodevelopment and Minimize Metabolic Risk
Study Design	Randomized, Controlled Trial
Primary Objective	The overall objective of the proposal is to demonstrate the feasibility of providing increased calories and protein in the first week of life to VLBW preterm infants.
Secondary Objective(s)	The secondary objective is to generate pilot data on the effects of this intervention on growth and neurodevelopmental outcomes.
Research Intervention(s)/Investigational Agents	Infants will be randomized to receive either standard parenteral nutrition via the NICU protocol or enhanced parenteral nutrition via the Study protocol during their first week of life through higher initial macronutrient provision and faster advancement of macronutrient provision.
IND/IDE # (if applicable)	N/A
Study Population	VLBW (birth weight <1500grams) preterm (gestational age (GA) at birth < 32 weeks) infants admitted to the University of Minnesota Masonic Children's Hospital NICU, for which written informed consent can be secured from a parent within 12 hours of birth.
Sample Size (number of participants)	80
Study Duration for Individual Participants	From Birth through 4 months corrected age for prematurity (6-8 months for most)

1.0 Objectives

1.1 The overall objective of the proposal is to demonstrate the *feasibility* of providing increased calories and protein in the first week of life to VLBW preterm infants, and to generate pilot data on the effects of this intervention on growth and neurodevelopmental outcomes. We hypothesize that infants receiving greater calories and protein in the first week of life will have improved FFM gains and higher levels of IGF-1 prior to discharge, and improved early cognition and faster speed of neural processing measured at term and 4 months corrected age (CA). To address these hypotheses, we propose the following specific aims:

Specific Aim I. ***Examine whether infants receiving earlier initiation of intralipids and more rapid increases in energy and protein intake during the first week of life ("enhanced nutrition protocol") have improved growth, indexed by increased FFM gains, compared to a standard nutrition protocol***. Body composition will be measured weekly using air displacement plethysmography (ADP) until discharge and at term and 4 months CA.

Specific Aim II. ***Determine if infants on the "enhanced nutrition protocol" have improved cognition and faster speed of processing at term and 4 months CA compared to a standard nutrition protocol.*** Neurodevelopmental outcomes will be measured using electrophysiologic (ERP) techniques.

Specific Aim III. ***To assess whether growth factors, including IGF-1 and IGFBP3, mediate the relationship between improved nutritional provision and improved FFM gains, cognition, and speed of processing in preterm infants.*** Growth factors will be drawn at 1 week of age and 35 weeks PMA.

2.0 Background

2.1 Significance: VLBW preterm infants commonly experience growth failure, most significantly in length and FFM, during their first weeks of life while they are sick and dependent on parenteral nutrition[1-5]. This growth failure is occurring at a critical time in brain development and has been shown to have a lasting negative impact on their neurodevelopment[4,6-7] The majority of these infants do not recover from this early growth faltering prior to hospital discharge, and in fact linear growth failure has been shown by our group to persist even beyond 2 years CA[1-4]. In addition to the neurodevelopmental consequences, early growth failure also increases these infants risk of developing later

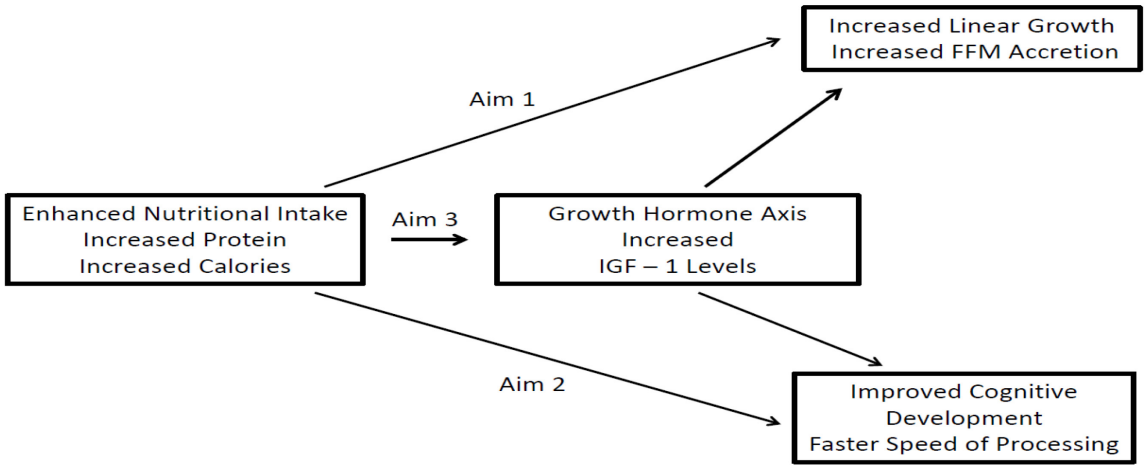
hypertension, insulin resistance, obesity and other components of metabolic syndrome, by necessitating later rapid catch-up growth in infancy and toddlerhood[8-11].

There are several factors contributing to this early growth failure, and many (e.g. illness and inflammation) of them remain largely out of our control. In contrast, nutrition is a factor the health care team can control, and early enhancements in nutrient provision may be our opportunity to prevent the above described early growth failure, improve neurodevelopment and optimize the later metabolic health of VLBW preterm infants. Multiple small retrospective studies have found significant decreases in growth failure (defined as weight z-score <10th percentile at discharge) after a slight change in their NICU parenteral nutrition protocol[12-15]. In addition, multiple groups have reported improved neurodevelopmental outcomes, including improved language scores[13], increased developmental quotient[16] and decreased incidence of brain lesions on MRI[17] in infants receiving more aggressive parenteral nutrition in the first weeks of life. Specifically, Stephens et al reported an increase of 4.6 points in the Mental Developmental Index (MDI) at 18 months for every additional 10 kcal/kg/day of energy provided in the first week of life and an 8.2 point increase in the MDI for every additional gram/kg/day of protein provided in the first week[18].

Despite the potential benefits, early enhanced macronutrient provision to VLBW preterm infants is not routinely practiced due to concerns about intolerance and toxicity. These concerns are based on older trials using different nutritional products than those routinely used in NICU's today. More recent studies (mostly small and retrospective) have found that earlier introduction and more rapid advancement of lipids and protein are safe, and in fact may decrease the incidence of hyperglycemia and parenteral nutrition associated cholestasis[14-15]. In addition, recent findings of increased adiposity among preterm infants at term CA has discouraged early enhanced nutrient provision based on a fear that this strategy, while being beneficial for the brain, will nonetheless lead to further increases in adiposity[11]. However, our group and others have instead found that increased nutrition provision, both in calories and in protein, leads to increased FFM gains, without accompanying increases in FM or adiposity[7.19]. Work under Specific Aims 1 and 2 will address this uncertainty through a comprehensive examination of both neurodevelopmental and metabolic outcomes (i.e., body composition) in a randomized nutrition intervention trial.

While the relationships between early malnutrition, poor growth and worsened neurodevelopment are relatively clear, the mechanisms behind these associations have yet to be elucidated. IGF-I is nutritionally regulated and negatively influenced by early malnutrition[12, 20]. Levels of IGF-1 play an important role in early postnatal growth, body composition and blood pressure in childhood, and improved neurodevelopmental outcomes among preterm infants[20-22]. Circulating growth factor concentrations, like IGF-1, are therefore potential mediators of the effect of nutrition intervention on diverse preterm outcomes, which hypothesis we are testing in Specific Aim 3. If this hypothesis is supported, IGF-1 could then be used as a biomarker for prediction of later outcomes and, relatedly, as a tool for monitoring the success of early nutrition interventions. In the future, development of a nutritional intervention that optimizes IGF-1 levels early in life for preterm infants could indicate whether or not the proper balance is being struck between adequate early FFM gains to optimize neurodevelopment and minimizing excess FM gains to decrease long-term metabolic risk.

In summary, recent neonatal literature continues to suggest the need for randomized trials of nutritional interventions that focus not only on weight gain, but more importantly on linear growth and FFM gains, and that can measure both neurodevelopmental and metabolic outcomes. Our expertise and experience in both neonatal body composition measurement AND methods of measuring early neurodevelopmental outcomes put us in an ideal position to trial an early enhanced nutrition intervention and potentially become a leader for future larger multi-center studies with long-term follow-up. This trial will not only allow us to determine the feasibility of providing additional nutrition to these sick infants, through close monitoring of metabolic tolerance (glucose, triglyceride and bilirubin levels) and careful detailed tracking of nutrient intake throughout their hospital stays, but will also provide us with preliminary data testing whether increasing all macronutrients incrementally shortly after birth eliminates early malnutrition, subsequent growth failure and neurodevelopmental delays.



2.2 Prelim Data: In our extensive prior work we have described differences in body composition between preterm and term infants, developed the first reference curves for preterm infant body composition, and shown relationships between early nutrition, illness and body composition trajectories through infancy among preterm infants. We were the first to describe associations between early FFM gains (not fat mass (FM) gains) and speed of processing and cognition. This observational work provides the necessary basis for our next phase of research aimed at increasing FFM gains prior to discharge and improving long-term growth, neurodevelopment and metabolic health for VLBW preterm infants through a randomized controlled nutritional intervention trial.

2.3 Innovation: The proposed pilot trial will be the first, to our knowledge, to comprehensively assess both infant metabolic (body composition) and neurodevelopmental outcomes following randomization to early enhanced nutritional intervention for preterm infants. In aim 1 we will examine growth, not only in weight and length, but also in different compartments (FFM and FM) during a critical time period of brain development using weekly ADP measurements. Given that FFM is considered a better marker of brain growth, and is associated with improved neurodevelopment, and increased adiposity a potential risk factor for later metabolic disease, using this more specific method of growth measurement allows a more comprehensive assessment of the risks and benefits of an early nutritional intervention. We will also continue to track gains in these compartments beyond hospital discharge until 4 months CA, allowing us to determine the lasting impact of this enhanced nutrition protocol. To our knowledge there is only one prior preterm nutrition intervention trial that assessed total body composition as an outcome and they were limited to two inpatient measures. In Aim 2, we will utilize ERP techniques to look specifically at the effects of early enhanced nutrition on neural speed of processing and early cognition. These techniques are more sensitive than standardized

developmental testing and will likely allow us to detect small, but potentially clinically significant, differences. In, addition, these techniques can be administered at younger ages than most standardized cognitive testing minimizing the effects of confounders such as parental education and home environment by allowing testing to occur closer to the administration of the intervention. Finally, these methods of testing are specifically targeting areas of the brain found previously to be impacted by early protein/nutritional status. Our previous observational work has established relationships between nutrient intake, FFM gains and speed of neural processing/cognition[7, 23]. To our knowledge there are no preterm infant nutritional intervention trials that have assessed early neurodevelopment using ERP. Aim 3 will allow us to begin to look at the mechanisms behind these relationships. Growth factors, especially IGF-1, are nutritionally regulated, associated with lean mass accretion, important for neuronal growth and differentiation, and have been found to be neuroprotective in preterm infants[20]. The proposed study will be the first nutritional intervention trial to assess growth factors, as well as neurodevelopmental and metabolic outcomes in preterm infants.

3.0 Study Outcomes

3.1 Primary Outcome: The primary outcome of this feasibility trial will be to determine if infants randomized to the enhanced nutrition protocol receive higher amounts of calories and protein throughout the first week of hospitalization.

3.2 Secondary Outcomes: The secondary outcomes will include measures of growth, neurodevelopment and growth hormone levels. Specifically, we will examine growth, not only in weight and length, but also in different compartments (FFM and FM) using weekly ADP measurements. We will also continue to track gains in these compartments beyond hospital discharge until 4 months CA. For neurodevelopment, we will utilize ERP techniques to look specifically at the effects of early enhanced nutrition on neural speed of processing and early cognition. Finally, we will look at the effect of early enhanced nutrition on IGF-1 and IGF-BP3 levels.

4.0 Study Intervention

4.1 Description: This nutritional intervention is designed to accelerate the addition of macronutrients over the first week of life to minimize the period of malnutrition, and is based upon the findings of numerous smaller, less comprehensive studies and expert opinion. Once consent is obtained, and the infant is admitted to the NICU, enrolled infants will be randomized to either receive parenteral nutrition per the standard NICU parenteral nutrition protocol or via the enhanced nutrition protocol for the first week of life via random envelope selection. Stratified

block randomization will be performed. Infants will be stratified by gestational age (22-25, 26-29, 30-32 weeks). Within each stratum, permuted block randomization will ensure that study personal are unable to predict treatment allocation. Infants randomized to the enhanced nutrition protocol will receive starter total parenteral nutrition (TPN) initiated at 80 mls/kg/day to provide protein at 4 grams/kg/day and a glucose infusion rate (GIR) of ~5.5 mgs/kg/min as soon as IV access has been obtained. Enhanced nutrition protocol infants will also be started on intralipids (IL) at 2 grams/kg/day once IV access is obtained. Infants randomized to the enhanced nutrition protocol will receive 4 grams/kg/day of protein throughout the first week of life. IL will be increased to 3 grams/kg/day on day of life (DOL) 2 and to 3.5 grams/kg/day on DOL 3. They will remain on this amount for at least the first week of life or until sufficient enteral feeding volumes have been established. GIR will be advanced by ~1.5 mgs/kg/min per day throughout the first week of life to a maximum of 12-14 mgs/kg/min. Again, they will then remain on this amount until sufficient enteral feedings have been established (typically approximately 1-2 weeks). Infants randomized to the standard nutrition protocol will receive macronutrients per the caregivers discretion, most commonly initiated with starter TPN at 60 mls/kg/day giving 3 grams/kg/day of protein and a GIR of ~4 and IL provided at 0-1 gram/kg/day. Advancement is most typically by 1 mg/kg/min per day for GIR and 1 gram/kg/day per day for IL and protein in the standard NICU protocol. Pertinent aspects of the differences in nutritional treatment in intervention and control groups are summarized in the table below

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
Control								
GIR	4.2	5	6	7	8	9	10	
IL (gm/kg)	0.5	1.5	2.5	3.5	3.5	3.5	3.5	
Kcals/kg	26	40	55	70	75	80	85	431 total Kcals/kg/week
								(avg 61.6 Kcals/kg/day)
Intervention								
GIR	5.5	7	8.5	10	11.5	12	12	
IL (gm/kg)	2	3	3.5	3.5	3.5	3.5	3.5	
Kcals/kg	47.5	55	77.5	85	92.5	95	95	547.5 total kcals/kg/week
								(avg 78.2 Kcals/kg/day)

*Each gm/kg of IL (Intralipid) provides 10 Kcals/kg
Each 1 mg/kg/min of GIR (Glucose Infusion Rate) provides ~5 Kcals/kg

5.0 Procedures Involved

5.1 Study Design: This exploratory study will use a simple randomized controlled trial design, and the parents, investigators, and all study

personnel (other than the in-patient study coordinator who oversees the ordering of the parenteral nutrition, the dietician and the data analyst in charge of assessing results of the study) will be blinded as to group assignment.

5.2 Study Procedures: Study Sample: Inclusions: We will include VLBW (birth weight <1500grams) preterm (gestational age (GA) at birth < 32 weeks) infants admitted to the University of Minnesota Masonic Children's Hospital NICU, for which written informed consent can be secured from a parent within 12 hours of birth. Exclusions: Infants who are diagnosed prenatally with a clinical condition (other than prematurity) that is known to affect growth rate, adiposity, or neurocognitive development, who experienced severe birth asphyxia, who are enrolled in another study affecting nutritional management, or who are likely to be transferred out of the NICU will be excluded from participation. We will attempt to enroll an equal number of female and male subjects, as well as those from a variety of racial and ethnic backgrounds.

Admissions to the antepartum unit and to the NICU will be screened daily by the inpatient research coordinator for potential eligibility for the trial. Once identified, the coordinator will present the mother/parents with a study brochure and offer to share more information and answer questions regarding the study if the family is interested. When possible, consent will be obtained prior to delivery. If unable to obtain consent prior to the infants delivery, the family will be approached within 12 hours of delivery to explain the study, answer questions and obtain consent. They will be allowed ample time to consider participation, as well as to ask questions of the clinical care team/ PI regarding the study.

Nutritional Intervention: Once consent is obtained, and the infant is admitted to the NICU, enrolled infants will be randomized to either receive parenteral nutrition per the standard NICU parenteral nutrition protocol or via the enhanced nutrition protocol for the first week of life via random envelope selection. Infants randomized to the enhanced nutrition protocol will receive starter total parenteral nutrition (TPN) initiated at 80 mls/kg/day to provide protein at 4 grams/kg/day and a glucose infusion rate (GIR) of ~5.5 mgs/kg/min as soon as IV access has been obtained. Enhanced nutrition protocol infants will also be started on intralipids (IL) at 2 grams/kg/day once IV access is obtained. Infants randomized to the enhanced nutrition protocol will receive 4 grams/kg/day of protein throughout the first week of life. IL will be increased to 3 grams/kg/day on day of life (DOL) 2 and to 3.5 grams/kg/day on DOL 3. They will remain on this amount for at least the first week of life or until sufficient enteral feeding volumes have been established. GIR will be advanced by ~1.5 mgs/kg/min per day throughout the first week of life to a maximum of 12 mgs/kg/min. Again, they will then remain on this amount until sufficient enteral feedings have been established (typically approximately 1-2

weeks). Infants randomized to the standard nutrition protocol will receive macronutrients per the caregivers discretion, most commonly initiated with starter TPN at 60 mls/kg/day giving 3 grams/kg/day of protein and a GIR of ~4 and IL provided at 0-1 gram/kg/day. Advancement is most typically by 1 mg/kg/min per day for GIR and 1 gram/kg/day per day for IL and protein in the standard NICU protocol.

Glucose, conjugated bilirubin and triglyceride levels will be monitored per standard NICU protocol and nutrition will be adjusted accordingly and insulin given per NICU protocol.

Nutritional intake will be recorded daily throughout the hopitalization, including kcal/kg/day and g/kg/day of protein by our NICU dietician. We will also gather data on days requiring TPN, type of feedings given (breast milk vs. formula) and degree of fortification (feeding additives). Following hospital discharge we will monitor intake through parent questionnaires monthly until the final (4 month CA) follow-up visit.

Growth and Body Composition Measures (Outcomes for Aim 1): Daily weights will be measured per unit protocol on an electronic scale to the nearest 1 gram. Weekly recumbent length (using an infant length board) and head circumference (using a flexible tape measure) measurements will be performed by a consistent measurement team to the nearest 0.1cm throughout their hospitalization, as well as at the term and 4 mo CA follow-up visits. Once clinically stable and able to tolerate room air for >5 minutes, we will begin measurements of body composition (FM, FFM and percent body fat) via infant ADP ("Pea Pod"; COSMED, INC, Concord, CA) by a trained NICU nurse, physician or research staff, and repeat these measurements weekly as tolerated. A detailed description of the Pea Pod's physical design, operating principles, validation and measurement procedures is provided elsewhere[24-28]. Briefly, the Pea Pod (1-8kg) measure the infant's volume using air-displacement plethysmography, and then calculates the density using the infant's mass and length. FM and FFM are then calculated using Fomon's model[29]. At a minimum, we plan to obtain one body composition measurement prior to discharge home from the NICU.

Families will be contacted monthly with study updates and general information on standard care of preterm infants following discharge to reduce loss to follow-up/maintain engagement in the study and will be scheduled for follow-up body composition and neurodevelopmental assessment at term (or as soon as possible post-discharge) and again at 4 months CA, when weight, recumbent length and head circumference will be measured, along with body composition using ADP. Raw body composition variables will be converted to z scores using our new preterm and term-corrected infant body composition reference data for ADP.

Neurodevelopmental Testing (Outcomes for Aim 2): Infants will be tested at term (or as soon as possible after hospital discharge) and 4 months CA; at both ages they will participate in a single one-hour session during which ERP data will be obtained. In order to obtain ERP data, infants will be fitted with a 128-channel Geodesic Sensor net. Once we have placed the electrode net on the infant's head, the infant will sit/lay on the parent's lap and an auditory oddball paradigm will be administered. The Mismatch Negativity (MMN) component is widely used in electrophysiological research to measure cognitive function; it is thought to represent perceptual learning and the detection of incongruence between two stimuli. The MMN is most reliably elicited by improbable, distinct "oddball" stimuli against a background of a repeating stimulus, and represents the comparison of the current auditory input to memory traces of previous inputs. The neural generators of the MMN component are widely distributed throughout the brain, and there is strong evidence to suggest that the frontal and temporal lobes are among them[30]. The University of Minnesota is one of only a few sites around the county with expertise in measuring cognition in early infancy using ERP technology, and one of the only who also has expertise in measuring infant body composition as well.

We will also use pattern-reversal visual evoked proteintals (VEP) at 4 months CA (type of ERP), which provides an early indication of neuronal speed of processing and myelination, which are critical to cognitive function. Infants will view a visual stimulus which consists of a pattern-reversing black and white checkerboard and VEPs will be recorded from ongoing EEG using the above mentioned net. As in our previous studies, the outcome variable with be the latency to the P100 waveform in msec[23].

Our prelimiary data has shown an association between speed of processing, cognition and FFM in other groups of preterm infants[7, 23], and thus we hypothesize that these findings will be robust amongst this population of at risk infants and potentially allow us to detect changes in cognitive measures related to enhanced nutritional provision. Our team in the CNBD has performed this testing on a variety of clinical populations (>500 infants) as well as healthy controls for over a decade[31-33].

Markers of Growth hormone axis activity (Outcomes for Aim 3): IGF-1 and IGFBP3 levels will be obtained in serum at 1 week of age and ~35 weeks CA. These specific markers were chosen as associations have been seen between linear growth, FFM gains, metabolic risk (e.g. increased adiposity and higher blood pressure), neurodevelopmental outcomes and IGF-1 and IGFBP3 in preterm born infants [12, 20-22]. IGF-1 and IGFBP3 will be analyzed by the Fairview Clinical Laboratory.

Additional Measures: The randomized design of this trial is expected to make the distribution of potential confounder values and characteristics similar in the intervention and control groups. Nonetheless, to confirm their equivalence and to describe the study sample, we will obtain birth anthropometrics, maternal age, education, and ethnicity, infant sex, gestational age at birth, weight-for-age z score at birth, and degree of illness from the medical record or parental self-report at enrollment. Degree of illness will be assessed using the Score for Neonatal Acute Physiology (SNAP) on DOL#1, 7, 14 and 21[34-35]. We will also collect data on other non-specific markers of illness, including days on the ventilator, requirement for blood pressure support, sepsis evaluations and antibiotic therapy, steroid administration, necrotizing enterocolitis (NEC), diagnosis of chronic lung disease and retinopathy of prematurity (ROP) etc. These measures will also allow us to track the safety of the intervention to ensure that rates of these common morbidities are similar in both groups.

5.3 Storage and Access: The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify the mother or baby as a subject. Any hard copies of the baby's research records will be kept in a locked desk in the locked office of the PI, co-I or study coordinator, and will be identified ONLY by an assigned study ID number (other identifying information will be removed). The study information will not be recorded in the medical record. These de-identified data will be entered into electronic format for storage and analysis; only the PI, co-Is, study coordinators and data analyst will have access to this electronic dataset.

6.0 Data and Specimen Banking

6.1 Storage and Access: Data from the various domains will be entered by the study personnel into a web-based secure database (RedCap) for storage, retrieval and analysis. This database will be password protected and only accessible to study personnel. The datasets will then be securely stored using Box.com per HRPP policy. We will need to download them to our University/AHC desktops for statistical analysis, however only a subset of the team will be given access to all files (study coordinator and PI) and the rest will have access to the deidentified files only.This data will be kept indefinitely to allow for the possibility of adding future study visits and/or future analyses. There will be no specimen banking.

6.2 Data: The full dataset for the study will be maintained as above, including demographic information, pregnancy history and ultrasound results, details of delivery, clinical history of infant including nutritional intake, blood test results, growth measurements and neurodevelopmental testing results.

6.3 Release/Sharing: Sharing of this data outside of our study personnel will only occur after appropriate IRB approval of additional studies or analyses. When possible, the data shared will be de-identified.

7.0 Sharing of Results with Participants

7.1 Results of routine laboratory tests will be shared with families in the usual manner per clinical routine. Weekly measurement results including body composition measurements will also be shared with families via a weekly measurement card for their records. ERP/VEP results will be shared with families who wish to receive them.

Families will be asked on the consent form if they wish to receive the study results when they are published. If they desire to receive the results, they will be emailed or mailed to the family per their preference when they are available.

8.0 Study Duration

8.1 Each individual participant in the study will be enrolled throughout their hospitalization and then out through their 4 month corrected age visit. For most patients, this will be a total of approximately 6-8 months. It is expected to take approximately 18 months to enroll all of the patients in this study. It is expected to take approximately 2 years to complete enrollment and all study visits. It will likely take an additional 6 months to complete data analysis.

9.0 Study Population

9.1 Inclusion Criteria: We will include VLBW (birth weight <1500grams) preterm (gestational age (GA) at birth < 32 weeks) infants admitted to the University of Minnesota Masonic Children's Hospital NICU, for which written informed consent can be secured from a parent within 12 hours of birth.

9.2 Exclusion Criteria: Infants who are diagnosed prenatally with a clinical condition (other than prematurity) that is known to affect growth rate, adiposity, or neurocognitive development, who experienced severe birth asphyxia, who are enrolled in another study affecting nutritional management, or who are likely to be transferred out of the NICU will be excluded from participation.

9.3 Screening: Admissions to the antepartum unit and to the NICU will be screened daily by the inpatient research coordinator for potential eligibility for the trial.

10.0 Vulnerable Populations

10.1 Vulnerable Populations:

☒ Children
☒ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☒ Non-English speakers
☒ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

10.2 Additional Safeguards: This study is aimed at optimizing the nutrition provided to preterm born neonates. Given this and the potential benefit to them they will be included in the study. Consent will be obtained from parents (mom and/or dad (if married)). Non-English speakers and illiterate persons will be included in the study, but not targeted, to allow for diversity in the study and equal opportunity for participation and potential benefit.

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented: We will plan to enroll approximately 80 infants in this study. We will potentially consent up to 100 infants, as some infants who are prenatally consented will no longer be eligible to participate in the study at the time of birth. For example, parents may give consent at 26 weeks gestation, but the infant may remain in utero until 33 weeks gestation, at which time they would no longer be eligible to participate.

12.0 Local Recruitment Methods

12.1 Recruitment Process: Admissions to the antepartum unit and to the NICU will be screened daily by the inpatient research coordinator for potential eligibility for the trial. Once identified, the coordinator will present the mother/parents with a study brochure and offer to share more information and answer questions regarding the study if the family is interested. When possible, and if there is IRB approval for this, consent will be obtained prior to delivery. If unable to obtain consent prior to the infant's delivery, the family will be approached within 12 hours of delivery to explain the study, answer questions and obtain consent. They will be allowed ample time to consider participation, as well as to ask questions of the clinical care team/PI regarding the study.

12.2 Source of Participants: The Epic (EMR) census for antepartum, labor and delivery and the NICU will be screened by the research coordinator.

12.3 Identification of Potential Participants: The unit census will be reviewed daily by the inpatient research coordinator to identify eligible patients. These patients will be drawn from the PI's patient population. Prior to birth, this will include mothers who have had a Neonatal Intensive Care Unit consult placed. After birth, parents whose infant is under the care of the PI and/or her colleagues will be approached. Patients will not self-identify, but rather will be approached based on eligibility criteria that is contained in the medical record (i.e. gestational age). The inpatient study coordinator will present the parent(s) with a brochure describing the study. Following this initial contact, the study coordinator will follow-up with parents at their convenience to describe the study in more detail and answer any questions before obtaining consent. The family will also have an opportunity to meet with the PI or another neonatologist if requested to answer questions regarding the study. Those patients who have "research opt out" in their medical record will not be approached for participation in this study.

12.4 Recruitment Materials: Parents will initially be given a study brochure that generally describes the study. If the parents are then interested in hearing more about the study, they will be given a consent form and a time to discuss the details of the study with the inpatient study coordinator, their care teams and/or the PI.

11.5 Payment: $25 Target gift cards will be given to each subject's parent at 3 time points (including discharge and the 2 outpatient visits).

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: There are no specific circumstances under which the infant will be withdrawn from the study without parental consent; however changes in the nutrition protocol for the study can be made at the discretion of the attending neonatologist. These changes will not preclude continuing in the study, but rather will be adjusted for when analyzing the study data. On the other hand, parents can withdraw their infant from the study at any time point.

13.2 Withdrawal Procedures: If the infant is withdrawn from the study prior to study completion (4 months corrected age), the data collected prior to withdrawal will be analyzed, but no further data collected.

13.3 Termination Procedures: If the infant is withdrawn from the study, the remainder of their NICU care will be per standard NICU protocol. Again, data collected prior to withdrawal will be analyzed, but no further data collected.

14.0 Risks to Participants

14.1 Foreseeable Risks:

Intolerance of IV nutrition: Preterm infants often experience hyperglycemia, hypertriglyceridemia and cholestasis (elevated direct bilirubin) while on total parenteral nutrition in the first few weeks of life. It is possible that rates or severity of these problems may be increased in infants receiving higher amounts and/or faster advancement of macronutrients. Infant's glucose, triglyceride levels and direct bilirubin will be monitored per the clinical routine which is at least daily for the first week of life for glucose, twice weekly for triglycerides and at least weekly for bilirubin. More frequent checks will be initiated, again per clinical routine, should infants show any signs of intolerance. Hyperglycemia often requires treatment with insulin in very low birth weight preterm infants, and infants in the study will again be treated per the usual NICU protocol at the discretion of the care team. In addition, macronutrient provision will be decreased per clinical routine should infants show these sign of intolerance. Two recent small studies have found that earlier initiation and more rapid advancement of these macronutrients actually result in less hyperglycemia/insulin use[14], similar rates of hypertriglyceridemia[14] and lower rates of parenteral nutrition associated cholestasis[15]. Therefore, an important aspect of this exploratory research project is to assess whether early initiation and more rapid advancement will lead to increased provision of macronutrients or whether the nutrition will have to be scaled back due to intolerance and result in similar nutrient provision.

15.0 Potential Benefits to Participants

15.1 Potential Benefits: There may or may not be benefits to receiving higher amounts of macronutrients during the first week of life. In a few small retrospective studies infants receiving higher amounts of nutrition in the first week of life had improved neurodevelopmental scores on standardized testing and improved growth, including improved head growth, increased amounts of lean mass and increased weight gain. Also, in a few small randomized trials infants had less hyperglycemia, and lower rates of cholestasis. Infants who are randomized to the enhanced nutrition protocol may experience these benefits.

16.0 Data Management

15.1 Data Analysis Plan: Data from the various domains will be entered by the study personnel into a web-based secure database (RedCap) for storage, retrieval and analysis. The NICU dietician is responsible for abstracting nutritional data from the electronic medical record (Epic). ADP data will be entered into the database by the study coordinators. ERP data will be abstracted by Neely Miller and cleaned of artifacts as previously described. The data analyst will examine each variable for outliers and distributional properties and flag and correct entry errors where possible

and will log-transform or otherwise normalize variables prior to analysis. From RedCap all datasets will then be securely stored using Box.com per the HRPP policy. They may need to be downloaded to University/AHC desktops for statistical analysis, however only a subset of the team will be given access to all files (study coordinator and PI) and the rest will have access to the de-identified files only. These laptops are password protected and maintained by the AHC. Although we do not anticipate many missing values in this short-term follow-up study, multiple imputation methods (e.g., Proc MI in SAS) will be used if missing data can reasonably be considered missing at random. Analyses will also be run without imputation and results compared. Analyses will be carried out using SAS version 9.4 (SAS Institute Inc.) using an intent-to-treat approach, with a 2-tailed $p<0.05$ as the threshold for statistical significance. For Specific Aims 1, 2, and 3, body composition data, neurodevelopmental outcomes, and IGF-1 and IGFBP3 will be treated as continuously-distributed variables assessed at multiple time points. For the ERP outcomes (which are measured twice), the primary hypotheses will be addressed using a simple general linear regression model for term-equivalent measures, and another similar model for 4 month corrected age measures, with assigned group as the independent variable in both cases. For FFM (with up to 10 repeated measures) and IGF-1 models, mixed effects regression models (using
PROC MIXED) will be used. The primary models will test assigned group (standard versus enhanced nutrition protocol) and assigned group x time interaction as the tests of differences in the group mean values for initial levels, and change over time, respectively, between intervention and control groups. To improve the precision of estimates, variables of interest (e.g., gestational age at birth, anthropometric z scores at birth, degree of illness, etc.) will be included in additional, secondary models. In addition, in Specific Aim 3, IGF-1 levels at both 1 week and 35 weeks will be examined as predictors of later neurodevelopment and body composition outcomes. IGF-1 will be considered a potential mediator of the intervention-outcome relationships if 1) the intervention is significantly associated with both IGF-1 levels and outcomes, 2) IGF-1 levels are significantly associated with FFM and neurodevelopmental outcomes, and 3) in a model that includes both IGF-1 and treatment group as predictors, the effect of treatment group on outcomes (mean differences) is diminished compared to results from models unadjusted for IGF-1. Other ways of assessing the possible role of IGF-1 in the treatment-outcome relationship will also be explored.

15.2 Power Analysis: A sample size of 40 infants in each treatment group (80 total) allows for up to a ~12% loss to follow-up after discharge and still have 35 infants per group. Our prior work showed a significant association of early nutrition (protein and calories in first week of life) with FFM gains throughout hospitalization ($p<0.01$ for both) in 34 VLBW preterm

infants[7]. We have also shown that higher energy (kcal/kg/day) across hospitalization was associated with faster speed of processing (shorter latency) in 16 preterm subjects[23]. We therefore expect that this pilot study, which is 2-3 times as large as previous studies, will be sufficient to produce statistically significant differences between groups. As this is a pilot trial, however, we have not conducted a formal power calculation. Rather, the results of this pilot exploratory study will generate estimates of effect size that will then be used to calculate sample size for our planned larger trial.

15.3 Data Integrity: Describe any procedures that will be used for quality control of collected data. All data will be stored in a RedCap database designed by the data manager for this study prior to data collection. All necessary medical record data (including the daily information on nutritional intake, procedures, and clinical outcomes, among others) will be abstracted by the clinical research manager on a weekly or biweekly basis. Body composition and ERP data will be exported in Excel format on a weekly or biweekly basis and shared on a password protected server with the data manager. While body composition data and ERP data go directly from Excel into RedCap, there is a possibility of data entry errors for the medical record data, and so the data manager or PI will conduct biweekly (initially) then monthly checks of data accuracy by comparing RedCap data against medical records data for validation in a subset of subjects. On a monthly basis, data quality will be examined for outliers and unusual values by the data manager, who will then communicate with the clinical research manager or other data collection personnel with access to the original data to resolve the errors and insure consistency in units and data collection processes.

17.0 Confidentiality

17.1 Each subject will be assigned a study ID number following randomization. A list of patient information and study ID numbers will be securely stored using Box.com per HRPP guidelines. Only members of the study team will have access to this link between the study ID number and other identifying information for the subject. This link is necessary in order that the infant's families may be contacted for future follow-up studies.

A copy of the consent form will be placed in the infants medical record after randomization occurs in order that all medical providers are made aware of the infants enrollment in the study. The study ID will not be recorded in the infant’s medical record.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring:

Independent monitoring of the clinical study for protocol, SOP, and regulatory compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the University of Minnesota's Clinical and Translational Science Institute (CTSI) monitoring staff. Utilizing UMN CTSI staff for this task ensures that only qualified monitors will be selected. Study monitors will review study materials (documents, records, Case Report Forms, etc.) to assure that the study is being conducted, recorded, and reported in compliance with FDA Good Clinical Practice. They will also ensure that the study is conducted in accordance with the protocol and inclusion/exclusion criteria as approved by the IRB.

The monitoring report will summarizes items reviewed during the monitoring visit. The summary will also include any data discrepancies/findings noted during the monitoring visit and the actions required by the study team to correct these discrepancies. The investigator will permit study monitors and appropriate regulatory authorities access to the study data and to the corresponding source data and documents to verify the accuracy of these data.

18.2 Data Safety Monitoring

Data Safety and Monitoring Committee (DSMC): An independent DSMC will be formed prior to the initiation of the study to monitor the progress of the study when 50% of the trial subjects have reached hospital discharge. The DSMC will include individuals with expertise in neonatology, biostatistics and clinical trials and will review accumulated blinded study data at the interim study point to ensure that the intervention is not leading to harm. The data they will review will included all labs related to nutritional tolerance as described above and other common co-morbidities of prematurity. The DSMC will not be charged with assessing efficacy before conclusion. Any adverse event, defined as a reaction or side effect that occurs during the course of the trial associated with the intervention, whether or not the event is considered related to the treatment or clinically significant will be reported to the appropriate institutional IRB and the DSMC. If the DSMC recommends modification or cessation of the study protocol at any time point, the IRB and the Department of Pediatrics (sponsor of the study) will be notified.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Parents of eligible subjects will be approached by the study coordinator and given a brochure. They will be asked for their permission to spend time reviewing further details of the study at a time convenient to them. Parents will be given the opportunity to ask questions and also to speak to a clinician (attending neonatologist or neonatal fellow) regarding the study prior to consenting to the study. Data gathered for the study will not be shared outside of the research team. Only data described in the HIPAA

form will be collected. Any questions that the parents feel uncomfortable answering can be omitted.

19.2 Access to Participants: The research team will only access information discussed in the HIPAA release form that was signed by the subject's parents. The research team has access to the data contained in the medical record as the PI is a caregiver for this patient population.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that your child has suffered a research related injury, let the study physicians know right away.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained): Consent will be obtained either prior to delivery or within 12 hours after delivery of the infant. Parents will be approached for consent either in the mother's inpatient room or in the NICU. They will initially be approached by the study coordinator and given a brochure generally introducing the study. They will be asked permission and also for a convenient time to discuss further details of the study and potentially obtain consent. If they are interested, they will be allowed ample time to look over the documentation and ask questions of the study coordinator. They will also be allowed to ask questions of their own care team and/or the NICU care team including the attending neonatologist or fellow on service. Consent will be obtained and documenting in writing on the approved consent form. A copy of the consent will be given to the family and also included in the infant's medical record.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Non-English Speaking Participants: Families who are non-English speaking will be included but not targeted. Languages for which short forms are available on the University of Minnesota IRB website will be included. Interpreter services will be used to review the consent form in detail with parents of potential participants. They will also be given an IRB approved short form and allowed ample time to ask questions with an interpreter present. Informed consent will be documented on the short form per IRB policy. Fairview Interpreter services will be used to ensure that qualified interpreters are utilized.

21.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): Participants in this study are neonates and are unable to provide consent. Consent will be obtained from their parent(s) (mother

and/or father if parents are married).

22.0 Setting

22.1 Research Sites: Admissions to the antepartum unit at the University of Minnesota Birthplace and to the University of Minnesota Masonic Children's Hospital NICU will be screened daily by the inpatient research coordinator for potential eligibility for the trial. Research procedures will be performed in the University of Minnesota Masonic Children's Hospital NICU while the infants are inpatient and in the Center for Neurobehavioral Development (717 Delaware Ave SE, Minneapolis, MN) as an outpatient.

23.0 Multi-Site Research

- N/A

24.0 Resources Available

24.1 Resources Available: Our 62 bed Level III NICU admits approximately 700 infants per year. We expect 100 infants per year to be eligible for the study, and participation rate is expected to be >70% based upon our past experience, yielding >80 subjects over 18 months. We anticipate that enrollment will take approximately 18 months based on enrollment rates in our previous studies, which will allow for completion of the 4 month follow-up visit within the two year time period allotted for this grant. We have enrolled ~50 patients in a 12 month period in a recent longitudinal study on VLBW's and ~120 infants in a 24 month period in a study on infant body composition after birth. We have a ~85% return to follow-up rate in our previous longitudinal study on body composition and speed of processing.

The infants will be monitored closely for any signs of intolerance and the neonatal care team including the attending neonatologist will have the ability to change the nutritional provision the infant is receiving if these signs are present.

All research staff will be adequately informed about the protocol, research procedures and their duties and functions. Nursing staff and other members of the care team will also be made aware of the protocol and research procedures and will have access to copies of the protocol for reference.

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