Study Title: Omega-3 Long Chain Polyunsaturated Fatty Acid (LCPUFA) Supplementation in Very Low Birth Weight Infants for the Prevention of Retinopathy of Prematurity

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN INSTRUCTIONS

These are instructions are for completing the Research Plan that is available in MS Word format from the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response in for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 05/11/2011

Protocol Amendment 6 dated April 1, 2016

1. PROJECT TITLE

Omega-3 LCPUFA Supplementation in Very Low Birth Weight Infants for The Prevention of Retinopathy of Prematurity: Proposal for a Prospective Randomized Controlled Masked Clinical Trial with Lipidomic and Transcriptomic Analyses

2. PRINCIPAL INVESTIGATOR

Shira L. Robbins, M.D.

3. FACILITIES

Neonatal Intensive Care Unit (NICU) at University of California San Diego Medical Center, Hillcrest and Jacobs Medical Center

4. ESTIMATED DURATION OF THE STUDY

5 years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Retinopathy of prematurity (ROP) is a blinding disease affecting infants born prematurely. These infants do not have enough essential fatty acids to structurally support the retina, the nerve tissue in the eye which allows us to see. A recent study showed that giving omega-3 (n-3) fatty acids to these infants soon after birth made them less likely to need invasive treatments for eye disease. We intend to give young infants born prematurely with n-3 fish oil treatment and look at how this changes factors in the blood that promote disease. We will do detailed blood studies comparing infants with and without ROP and will follow these infants over time to assess their eye development.

6. SPECIFIC AIMS

The purposes of this study are the following:

- To differentiate the phospholipid profiles and gene expression pathways of at-risk very low birth weight infants with and without treatment with Omegaven® (high n-3 fish oil supplement)
- To establish whether omega-3 fatty acid supplementation in extremely low birth weight infants will reduce the incidence and severity of retinopathy of prematurity (ROP)

7. BACKGROUND AND SIGNIFICANCE

Clinical:

Approximately 517,000 infants are born prematurely every year[1], and as low birth weight and premature infants are surviving longer, they are at high risk of developing severe ROP. In the United States, 2,000 infants per year are diagnosed with severe ROP, which is the leading cause of irreversible childhood blindness in the United States. In our NICU, we care for between 60 and 80 infants each year that are born with low birth weight.

Usual parenteral nutrition protocols do not meet the infants' fetal accretion rates. Despite receiving 14-28 mg DHA/kg/day,[2] preterm infants have lower serum DHA and EPA levels than they would have had *in utero*, and

their tissues have lower n-3 and n-6 fatty acid than full term infants, indicating that their dietary needs are often not met.[3] Preterm and small for gestational age infants have altered serum phospholipid fatty acid profiles with lower DHA and polyunsaturated omega-3 fatty acids than appropriate for gestational age infants.[4] Low birth weight infants often have severe lung disease and are exposed to exogenous oxygen, which causes retinal blood vessel attenuation, retinal hypoxia, up regulation of pro-angiogenic factors, and neovascularization, which can lead to irreversible vision loss.

In a recent Polish prospective interventional study, Pawlik et al. showed that in preterm infants (average 28 week gestation, 935 gram birth weight), continuous intravenous n-3 fatty acids with Omegaven® from day one to day 28 of life, followed by enteral omega-3 fatty acids is safe and resulted in a significantly decreased need for ROP laser treatment. In the treatment group, 9 of 60 infants needed laser compared with 22 of 70 infants in the control group.[7,12] On treatment, infants had higher plasma and red blood cell DHA levels at 7 and 14 days and a lower risk for cholestasis. This study showed that treatment was well tolerated in preterm infants and that Omegaven® has a positive effect on ROP pathogenesis, but no investigations were done into the mechanisms by which ROP was suppressed in the experimental group compared with the control arm. There is also no clinical data that currently differentiates the differences in the blood biology (fatty acids, gene expression, and proteins) in infants with and without severe ROP.

Translational:

An oxygen-hypoxia-ischemia mouse model of ROP was developed and used to examine the effects of n-3 PUFA rich (Japanese) and n-6 PUFA rich (western) diets on retinal vascular development in a model of severe ROP. The study showed that there was less retinal vascular obliteration and neovascularization in pups raised on a diet with 2% total fatty acids with n-3s with a 1:1 ratio of DHA: EPA in contrast to a diet in which the 2% total fatty acids were consistent with n-6 fatty acids.[4] The n-3 diet had a 50% protective effect against pathologic neovascularization due to increased regrowth of vessels after vessel loss,[6] and this was replicated by giving downstream mediators of n-3 fatty acids (resolvins and neuroprotectin). Inflammatory mediators, including TNF-α, were also lower in the n-3 group, and neovascularization was attenuated via a *PPAR-γ* (independent of VEGF).[7,2] In mice, EPA supplementation has been shown to increase serum IGF-1, correlating with less risk for ROP. n-3s are a new target for ROP treatment.[8]

Basic:

Docosahexaenoic acid (DHA), a vital dietary long chain polyunsaturated fatty acid (LC-PUFA) is a key component in the sensory and vascular retina. Eicosapentaenoic acid (EPA), a substrate for DHA, is the parent fatty acid that affects eicosanoids implicated in abnormal retinal neovascularization, vascular permeability, and inflammation.[9] EPA depresses vascular endothelial growth factor (VEGF)-specific tyrosine kinase receptor activation and expression, a key driving force in the pathologic neovascularization.[9] DHA is antinflammatory, neuroprotective, and also protects against neovascularization.

Safety:

In the recent Polish prospective interventional study, Pawlik et al. showed that in preterm infants (average 28 week gestation, 935 gram birth weight), continuous intravenous n-3 fatty acids with Omegaven® from day one to day 28 of life (n=60), followed by enteral omega-3 fatty acids is safe, and no adverse events or increase mortality or morbidity was noted in the treatment group.[7,10] At the Children's National Medical Center in Washington DC, Omegaven® was given to ten premature infants with a median gestational age of 26.4 weeks (range, 23.7–34.0 weeks) with hyperbilirubinemia. They showed that the treatment was well tolerated, and there were no adverse events.[11] The drug Omegaven is now FDA approved but not for the use specified in our study.

In a recent Cochrane review, LC-PUFA supplementation is considered safe in preterm infants with no increase in morbidity or adverse events.[2,12,13,14,15,16,17,18]

8. PROGRESS REPORT

Not Applicable; this is a new study

9. RESEARCH DESIGN AND METHODS

The treatment duration for the study will begin 0-7 days of life and continue until 40 weeks adjusted age (full-term). Intravenous treatment will start in the first few days of life and will continue until the infant can tolerate enteral nutrition. Once enteral feeds can be started, supplementation by mouth will begin until 40 weeks adjusted age.

Laboratory blood draws:
Prior to enrollment: In addition to routine tests, blood will be tested for AST and ALT. If these tests are interpreted as abnormal, the infant will not be considered for enrollment in the study as it will be deemed a contraindication to supplemental Omegaven.
While the infant is growing in the hospital, the doctors will need to check the infant's blood to make sure the infant is developing as expected.

If the infant is enrolled in the study, the infant will be randomized in blocks of 4 by gestational age to one of two groups. The control group will get standard of care nutrition, and the experimental group will get standard of care nutrition with supplemental omega-3 fatty acids. Soon after birth, most premature infants need additional nutrition through the vein (intravenous). For the control group, there will be no changes to the standard of care parenteral nutrition. For the experimental group, the infant will receive Omegaven, an intravenous lipid preparation prepared from highly refined fish oil, in addition to the standard of care parenteral nutrition. In the instance that twins are enrolled in the study, the siblings will be randomized as one to receive the same treatment per request and approval from Dr. Kim.
Transition – For the second/interventional group, Omegaven will be stopped once enteral feeds are at 120 ml/kg and enteral Oil will be started. There will be no overlap of parenteral and enteral n-3 supplementation.

If the infant can start using his/her own stomach for digestion, he/she will get fatty acid supplementation. In the control group, the infant will receive standard of care feeding. If the infant is in the experimental group, the infant will get one fourth (1/4) teaspoon per kilogram per day (1.25mL/kg/day = 400 mg omega3 per kg of fish oil per day) of Carlson's fish oil oral solution. Dose will be divided to at least twice a day dosing for better tolerance.

Fatty acid supplementation will continue until the baby is full term (40 adjusted weeks of age). If the infant is discharged before he/she is full-term, the infant will be sent home with a bottle of the fatty acid oral solution for the infant to continue daily until he/she is full-term (40 weeks of age). The infant's nutritional needs will be carefully monitored by his/her doctor and nutritionist per NICU protocols.

To monitor the amount of fatty acid nutrition getting into the blood, we will check the infant's blood. As much as possible, we will coordinate the study blood collection at the same time as the routine NICU blood draws. We will collect 1.3 milliliters of blood at 4 different times spread apart while the infant is in the hospital. At each time point, we will collect about 1/4 teaspoon of blood, for a total of about 1 teaspoonful.

The blood draws will occur as the following four time points:

- Blood draw T0= Prior to parenteral nutrition, within 1st 3 days of life. This blood collection should be

taken from cord blood. If cord blood is not available, sample will be collected from a UAC, UVC, or peripheral blood draw concurrent with SOC.

- Blood draw T1= 5 days after parenteral nutrition is started; grace period +/-3 days therefore total 2-8 days after parenteral nutrition started.
- Blood draw T2= 5 days after enteral nutrition full feeds have arrived; grace period +/-3 days therefore total 2-8 days after full enteral nutrition arrived.
- Blood draw T3= Prior to discharge from hospital coinciding with time that ROP may be present, ≥35 weeks adjusted age.

This blood will be used for looking at what new genes (mRNA) the infant is making and to check how many and what kind of fatty acids the infant has in the blood. Before testing, the blood will be stored in a storage facility at the UCSD Department of Ophthalmology Blood Bank and labelled with a barcode without the infants' personal information. This is not the infant's DNA, and no DNA will be isolated or tested. Samples will be stored for 10 years. After this time point, all samples will be destroyed if not used by that time. If the parent decides to withdraw consent the blood samples that were already drawn will be destroyed, however, any previously obtained data from sample testing will be kept.

We will examine the infant's eyes according to the standard NICU guidelines and protocols. We will also examine the infant's eyes in our eye clinic after discharge over time as we do for all premature infants to support the infant's visual development.

During the study:
Maternal diet questionnaires will be administered to the maternal subjects following enrollment. This questionnaire is the Omega 3 Fatty Acid Questionnaire and has been validated in a related study for this fatty acid[19]. It is anticipated to take 10-15mins to complete. Mothers will be asked to complete this questionnaire at the time of enrollment.

Blood samples will be collected 4 times. When possible, and in the majority of blood draws, 1.3 cc of whole blood will be collected at the same time as other blood draws to avoid multiple sticks. Whole blood will be collected in a green or lavender top tube. One hundred µl of plasma will be isolated, and this will be aliquoted into in two tubes and frozen (-80ºC).

Lipidomics: Plasma fatty acids will be tested using a preprandial whole-blood sample (1.3 mL) drawn 2–4 hours after the parenteral nutrition (PN) had ended for the day and after enteral feedings were held for 3 hours if the patient was also fed enterally. The schedule for sampling will be as follows: prior to parenteral nutrition within ≤ 3 days of life; within 5-8 days after parenteral nutrition is started; within 5-8 days after enteral nutrition full feeds is started; and prior to discharge from hospital coinciding with time that ROP may be present. The samples will be sent to Dr. Metallo's Institute of Engineering in Medicine Laboratory at UCSD or another UCSD laboratory for internal validation of assays. Dr. Radha Aayagari's lab (UCSD Department of Ophthalmology) or another laboratory with similar capabilities will perform some of the RNA isolation and analysis. Capillary gas chromatography/mass spectroscopy will be the one of the main methods used to determine the phospholipid profile.

Transcriptomics: From the plasma isolated from the whole blood samples, 50µl will be used for mRNA isolation. This will be collected and frozen as the study is ongoing. The fold expression of genes associated with the fatty acid synthesis pathway, hypoxia and pro-angiogenic pathways will be correlated with clinical disease.

Eye exams**:** All infants will get eye exams according to standard NICU protocols. Serial eye exams will be performed according to the usual intervals, which is until retinal vascularization has matured or active ROP has stabilized, usually at 1-2 months post-term. The area of vascularized retina, clock hours of neovascularization, and amount of retinal vascular dilation and tortuosity will be measured by indirect ophthalmoscopy in all infants at each clinical exam by an ophthalmologist masked to the treatment group**.** Stage of retinopathy of prematurity and need for ROP treatments will be measured at 40 weeks gestation plus or minus three weeks and followed over time. Infants with ROP will be monitored over time for longer term visual and anatomic outcomes. For both groups, infants will have SOC eye examinations prior to discharge around 40 weeks GA (≥38 wks GA). For both groups, if infant is discharged prior to 38 weeks GA, we will collect follow-up data from their outpatient follow-up eye exam from UCSD or other provider

Nutrition: Omegaven has been approved by the FDA for use in children and infants with parenteral nutrition associated liver disease (PNALD). In this study we intend to use Omegaven under an IND exemption to study the use of the drug in reducing the incidence and severity of retinopathy of prematurity (ROP). Our aim is to differentiate the phospholipid profiles and gene expression pathways of at-risk very low birth weight infants with and without treatment with Omegaven® (high n-3 fish oil supplement) and to establish whether omega-3 fatty acid supplementation in extremely low birth weight infants will reduce the incidence and severity of retinopathy of prematurity (ROP). The study intervention "drug product" has been used in the neonatal population via the same route of administration safely for other disease indications internationally and nationally including here at University of California San Diego. This investigation does not significantly increase the risk or decrease the acceptability of risk of our study population.

Infants in the experimental group will be getting Omegaven® for parenteral nutrition in addition to the standard nutritional requirements (Intralipid within a 3:1 TPN). Omegaven dose will be dosed per weight to give goal dose of 1 g/kg/day infused over 12 to 24 hours with the intention to run over 24 hours. Initial Omegaven dose will be between 0.5 g and 1 g/kg/day. If the infant's nutritional lipid requirements are for more than 1g/kg/day, the remaining calories from fat in the experimental group will be derived from Intralipid (the parenteral lipid emulsion used most often in the UCSD's NICU). Additional triglyceride testing should not be necessary given dosing[20].

Infants in the control group will be getting the standard of care, which is Intralipid® combined with the standard nutritional requirements in a 3:1 TPN. Intralipid will be used according to the Dosage and Administration information in the package insert up to 3.5 g/kilo/day. Initial dose is between 0.5 g and 1 g /kg, starting at 18:00 and running for 24 hours. Total daily dose will be infused over 12 or 24 hours based on provider preference.
Once enteral nutrition reaches desired minimum mL/kg/day (determined by the NICU neonatology team), then parenteral supplementation will be discontinued and enteral supplementation will begin. Carlson's Fish oil ® (400 mg of omega 3 fatty acids: EPA 200 mg, DHA 125 mg, and 75 mg of other omega-3 fatty acids per ¼ tsp) will be given in the experimental group. Enteral fish oil supplementation of 1.25mL/kg/day (1/4 teaspoon per kg per day) divided at least every 12 hours for tolerance will be continued until the baby is at 40 weeks adjusted age or the retina is fully vascularized. We will adjust our fish oil dosage to maintain maximum enteral DHA supplementation to 125 mg/kg/day (omega3 400mg/kg/day). The total dose will be given BID initially. If there are any symptoms of GERD or other intolerance symptoms that are concerning to the primary team, then oral fish oil total daily dose will be divided over multiple administrations. If enteral oil is not tolerated even after medical management, we can decrease the amount by 25% until tolerated. We do not expect poor tolerance to this dose given 120 mg/kg/day has been tolerated as an emulsion via feeding tube without any complications[21].
As it is typical of this study population to require varying needs of care and drug administration, should any infant randomized to the Omegaven arm require discontinuation of the study drug for clinical reasons for more than

five days (either consecutive or accumulative), that infant will be withdrawn from the study. Drug administration disruptions occurring for 5 or less days (total) shall not be considered protocol deviations but will be recorded and noted in the annual FDA safety report.

Following discharge from the NICU and prior to infants reaching 40 wks, a research team member (other than the PI) will contact the parents with infants in the Omegaven arm once weekly to encourage parents to continue with the prescribe fish oil administration for their infant until he/she has is 40 weeks adjusted age.

The investigational drug pharmacy (IDS) will obtain the Omegaven and dispense it to the nurse for administration in a separate line than the rest of the nutrition (amino acids, sugars, etc). The NICU nutritionist will optimize the total nutritional calories to the infant per NICU protocols. The IDS pharmacist, nutritionist, and NICU team will not be blinded to ensure that the infant in the Omegaven group meets all the nutritional requirements as determined by the NICU neonatology attendings and fellows involved in the study. The ophthalmology team will be blinded to the treatment group to prevent any potential for bias during the eye exam.

Outcome Measures:

Outcome 1: Change in concentrations of basic fatty acids (EPA, DHA, and AA) and their bioactive metabolites will be assessed at multiple time points.
Outcome 2: Change in mRNA expression of TNF-α, PPAR-ɣ, and VEGF at multiple time points.
Outcome 3: Severity stage of ROP in Group 1 compared to Group 2. This will be assessed at the time of ROP screening (approximately 31 weeks), and the outcome will be measured at approximately 40 weeks adjusted age. The stage of ROP at 40 weeks adjusted will be used for statistical analyses.

Safety:
A data safety monitoring board (DSMB) will be established to monitor the safety of enrolled infants in the study as well as identifying the efficacy of the treatment at ongoing intervals. The DSMB will meet after the first 5 infants are enrolled and then regularly at multiple intervals during the study. Clinical safety assessments will occur during the hospital admission including vital signs, weight, physical exam and laboratory assessments of triglycerides. The neonatologist will review the assessments and determine if the subject should remain in the study or be removed.

Statistical Analysis
Our primary analytic approach will use generalized linear mixed models (GLMM). These methods will address problems of missing data, variable timing of the subject visits, and other possible unintended violations of design. Although our retention and follow-up plan is designed to minimize missing data, an advantage of the GLM models is that they allow us to maximize statistical power by not excluding subjects with some missing data. More specifically, GLM assumes that the data can be missing at random (MAR) or missing completely at random (MCAR). The benefit of this assumption is with a repeated measure problem (e.g., longitudinal data) you can still analyze data from all subjects, even if some have missing data (assumed MAR or MCAR). Mixed regressions will also allow us to estimate an intercept and slope for each patient based on all available data for that individual augmented by the data from the entire sample, with two random effects being used to model time trends (i.e., a random intercept and a linear trend). Further details of selected analyses related to each outcome are provided next.

For Outcome (a-b), the primary outcome is DHA at a specified period of time (i.e. 40 weeks) to assess the basic fatty acids. Outcome (a) posits that patients in Group 1 will differ from those in Group 2 with respect to i) DHA

ii) EPA iii) AA iv) bioactive metabolites. To assess Outcome (a) (i.e. to evaluate the effects of group, time, and their interaction on the change from baseline DHA measurements), a mixed effects model with group (IV Omegaven then PO baby fish oil or Intralipid), time, and group by time interaction as fixed effects, and random intercept and slope to account for within subject correlation. We expect that the interaction in question will be significant.

For Outcome (c), we hypothesize that Group 1 and Group 2 will have a different severity stage of ROP. To assess Outcome (c), we will use a *Mixed*-effects *ordinal logistic regression model* with severity stage of ROP after 40 weeks (Stage I, II, III, IV, V) as the outcome variable. The same fixed and random effects mentioned above will be used in evaluating Outcome(c).

All statistical analyses will be performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina, USA).

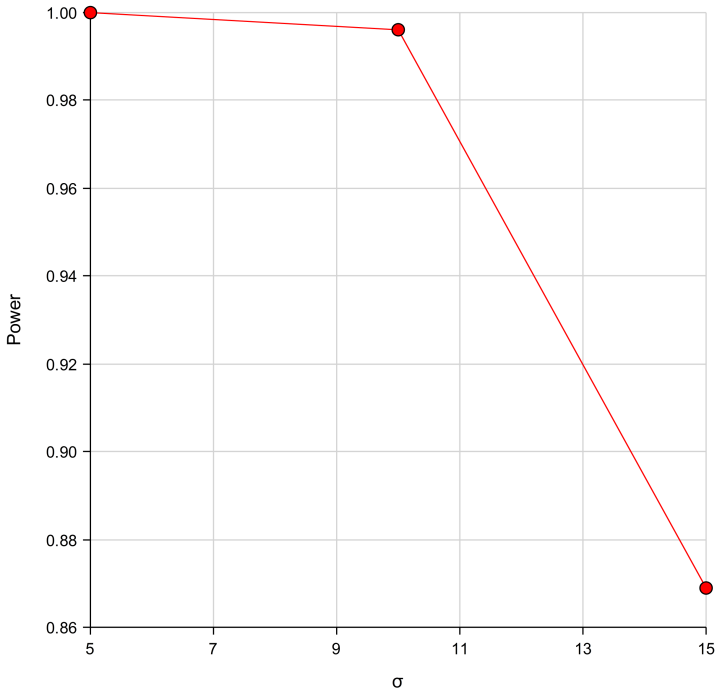
Power Calculations

The power calculations that follow were conducted using the software PASS and are based on two-sided tests, with a 0.05 type I error rate. A sample size N=40 was assumed. Power calculation for the primary outcome is presented below.

Power for Outcome (a)

Outcome (a) tests the effect that Group 1 has a different average DHA measurement compared to Group 2. The power calculation for Outcome (a) was based on a two-sided two-sample t-test with a dependent continuous variable (i.e. pre-post difference in DHA measurements) on a categorical independent variable (i.e. Group 1 and Group 2) with a sample size of 40 total subjects. These subjects were equally distributed between each of the two treatment groups. In Pawlik et al. (2013), the mean pre-post difference were 42 μmol/L for patients in Group 1 and 27 μmol/L for patients in Group 2. Following Pawlik et al.'s sampling distribution, we also considered 6 common standard deviation estimates for the power calculation 5, 7, 9, 11, 13, and 15. It should be noted that as the common standard deviation within the group decreases, the group will yield greater power to detect an intervention group effect. As illustrated by the curve in Figure 1, we will have over 80% power to detect a mean difference among the 2 groups of average DHA measurements with a common standard deviation of 15, which is the smallest difference that we can detect with the proposed sample size.

Figure 1: Power for Group Effect on the DHA at 40 weeks.



Note: Even though the data analysis plan relies on longitudinal methods (GLMM), due to unavailability of estimates for repeated measures, the above power calculations were based on a single time point method (two sample t-test). However, the use of a longitudinal method generally results in an increase in power, therefore we believe we will retain sufficient power for the study based on the methods proposed here.

In addition, we have determined that in order to reach a targeted sample size of 40 subjects completing treatment, we will need approximately 60 subjects enrolled to this protocol. This is our target accrual.

10. HUMAN SUBJECTS

The University of California, San Diego (UCSD) is the only site participating in this study.

We anticipate enrolling 60 infants and up to 60 mothers at UCSD. We will consider patients for enrollment into this study for 5 years.

INFANT:

Inclusion Criteria:

- Infants born ≥ 23 weeks gestation and ≤ 30 weeks gestation or less than 1500 g at birth.
- Infant whose parent or guardian signed the written consent and HIPAA form.

Exclusion Criteria:

- Patients with liver disease attributable to known causes (i.e. genetic disease, hepatitis) and/or bleeding or clotting abnormalities will be excluded as shown by LFTs.
- Infants < 23 weeks gestation

MOTHER:

- Any mother 18 years of age or older that allows their infant to be enrolled.
- Proficiently English speaking/reading and can complete questionnaire

Infants may still be enrolled in this study if the mother declines to be also participate in the study.

Participation in research is entirely voluntary. Parents of subject may refuse to participate or withdraw at any time without penalty or loss of benefits to which they are entitled. If the parent of subject decides that he/she no longer wishes to continue in this study, the subject's parents will be required to notify the study doctors, Dr. Robbins or her research staff by calling her at (858) 822-4333.

The study doctor may decide to take the subject off of the study without the parent's consent if:

- Subject is unable to meet the requirements of the study;
- Subject's medical condition changes;
- New information becomes available that indicates that participation in this study is not in the subject's best interest;
- If the study is stopped,
- The sponsor of the study or the competent authority has the right to withdraw the subject from the study without the parent's permission,
- The study physician can withdraw the subject from the study without the parent's consent if he/she comes to the conclusion that further participation is not in subject's best interest. This can be due to disease or side effects or because subject does not comply with study procedures

11. RECRUITMENT

Waiver of Consent for Aiding in Research Recruitment:
I am asking for a waiver of consent while recruiting subjects because:
It would be minimal risk to the potential subjects while reviewing their private information. For this study, the subjects will already be hospitalized. The PI or sub PI will need to review the subjects' medical records for their routine care and to determine treatment for the subjects. While reviewing the medical records for their standard of care (SOC) treatment, the PI or sub PI may determine that the subject may qualify for the study and then proceed to ask the subject if they would be interested. The PI or sub PI will not review a patient's medical record solely to determine if they qualify for this study.
Reviewing patients' medical records would not adversely affect the rights and welfare of the potential subjects because the patients have already signed a HIPPA form when they were admitted to the hospital. Because the patient signed the form, we are allowed to review their medical records.

We would not be able to determine if the patient qualifies for this study without reviewing their medical records.

We will provide any new pertinent information to the subjects by providing the subject an addendum consent form with the information about this study. The patient will have time review and ask questions before signing the addendum and will be able to withdraw their consent if they desire.

I am asking for a waiver of HIPAA Authorization while recruiting subjects because:
The research staff will only print out medical records from patients when they have signed the consent form and the HIPAA consent form. If we do print out medical records, we will immediately black out any PHI on the documents, then copy the documents, and then again black out any PHI. The charts will be kept in a locked office in a locked cabinet and only the research staff assigned to the study will have access to the charts.

We would not be able to determine if the patient qualifies for this study without reviewing their medical records including their PHI (for example we will need contact information and mailing information).

The benefit of allowing access to the patient's PHI, will allow us to determine if they qualify for this study (for example their birth weight or gestational age).

The PHI that we will be used for this study may include the infant subject's DOB, telephone number, age, address, and name. The sponsor will not have access to the patient's PHI. Only the PI, sub PI, and the study coordinator assigned to the study will have access to this information.
Subject's parents will be asked to provide written consent, using an IRB-approved consent form. The consent process will take place prior to performing any study related procedures. The Investigator, sub PI, or study coordinator will describe the study, including detailed information about risks and benefits, to potential subject parents. The PI, sub PI, or study coordinator will determine if the subject's parents understands the study before they sign it by administering a post-consent quiz to determine if they understand.
The parents of potential subjects will be encouraged to take as much time as they need to discuss the study with the subject's personal physicians, family members and friends. The parents will be encouraged to take the form home with them. It will be made extremely clear to the parents, if applicable, that there is absolutely no guarantee that the subject will benefit personally. The parents will be encouraged to ask questions. Before signing of the consent form, the study doctor or study coordinator will ask questions to the subject's parent to confirm that he/she fully understands the potential risks and discomforts, and has a realistic understanding of potential benefits. The informed consent will be obtained in the mother's hospital room, after the parents determine if they are interested in possibly participating in this study.

As this research is subject to HIPAA privacy rule provisions, subject's parents will also be requested to sign a separate authorization for the use of protected health information (i.e., HIPAA form specific to the research study). The investigator or study coordinator will obtain informed consent in a language understood by the prospective participant.

12. INFORMED CONSENT

Parents of potential subjects will be asked to provide written consent, using an IRB-approved consent form. The consent process will take place prior to performing any study related procedures and in a private location. The potential subject will already be admitted to the hospital. The Investigator or study coordinator will describe the study, including detailed information about risks and benefits, to the parents of potential subjects. The investigator or study coordinator will provide the parent with an IRB-approved consent form. Parents will be given ample time to read this consent form at the same visit or may take it with them to read at another time. Parents will be given the opportunity to ask and receive answers to all questions they may have about the study, its risks and benefits, or the consent form itself before signing the consent form. As this research is subject to HIPAA privacy rule provisions, participants will also be requested to sign a separate authorization for the use of protected health information (i.e., HIPAA form specific to the research study). The investigator or study coordinator will obtain informed consent in a language understood by the prospective participant or their legally authorized representative, using certified translations of study documents and qualified translators, where applicable.
For the follow-up eye exam data, we will obtain a signed medical release authorization form for any patients scheduled to receive an exam outside of UCSD as their SOC.
Subjects who fulfill the eligibility criteria will be offered further participation in this study. Only subjects who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., subjects initials, study numbers, etc.) recorded on the Screening/Enrollment Log.

All signed consents will be maintained in marked binders, secured in locked filing cabinets within private administrative offices at UCSD's Clinical Teaching Facility on campus accessible to study coordinators and principal investigators only.

A copy of the HIPAA authorization and informed consent form(s) that will be used on this study are attached to this IRB application for your review.

Oral consent will be obtained from the maternal subjects for completion of the maternal questionnaires. No PHI will be collected from the mother nor will her medical records be accessed.

13. ALTERNATIVES TO STUDY PARTICIPATION

An alternative to this study is not to participate in this study. Subjects may or not receive benefit from this research study. However, the information we obtain from this study may help us to treat patients with ROP more effectively in the future.

14. POTENTIAL RISKS

There may be risks, discomforts, or side effects that are not yet known.

Possible Risks of Blood Drawing:

The drawing of venous blood is a routine medical procedure practiced daily by medical personnel. There are only very minimal risks involved in the drawing of a blood sample. Occasionally bruising may occur near the insertion point, which is generally quickly healed by the body. In order to avoid this hospital staff will gently press for a few minutes on the compression bandage applied to the insertion point. There is a possible risk of anemia which could contribute to the need for blood transfusion though many very low birth weight infants require a transfusion regardless of their participation this study. Accordingly, if transfusion is needed the additional exposure to blood products is noted. Blood draws can lead to rapid changes in hemodynamics of very small infants although this is not expected. Extremely rare injury to the vessel wall or a nerve may occur. In extremely rare cases, although sterilised needles are used and the skin is disinfected before insertion of the needle, infection may occur. This usually is quickly healed by the body and only in rare cases is an antibiotic required. In very rare cases a blot clot can form. These are the same risks that occur with all blood draws that occur as part of the usual care to support a premature infant.

Other Risks:

Because this is a research study, there may be some unknown risks that are currently unforeseeable. Parents of subjects will be informed promptly of any significant new findings.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Adequate measures have been taken to minimize all of the above risks prior to initiation of this study, including proper design specification and review, preclinical testing, and clinical evaluations. The study doctor will provide appropriate training to the research staff prior to our study initiation.

Safety assessments will include vital signs, weight, physical exam and safety laboratory assessments. The PI or sub-PIs will review the assessments and determine if the subject should remain in the study or be removed.

Loss of Confidentiality:

There is a risk of a loss of confidentiality if information on the study is lost or stolen. Every measure will be taken to ensure confidentiality. The chance of a loss of confidentiality occurring during this study is highly

unlikely. However, there is a potential risk of loss of confidentiality by participating in this study. Research records will be kept confidential to the extent provided by law. It is however, always possible that the information in the research records could become known outside of the research setting. To minimize this risk, all records which identify the subject will be stored in a locked file cabinet in a locked office and will only be accessible by study staff. Computers used to store subject's information are password-protected and only accessible by study staff.

A Data Safety Monitoring Board (DSMB) will be created. The function will be to monitor data regarding safety of the treatment in enrolled infants as well as identifying the efficacy of the treatment at ongoing intervals.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Absolute confidentially cannot be promised because information needs to be shared as described below. However, information will be collected and shared following standards of confidentiality. Subjects' identity as a participant in this study will remain strictly confidential. Subjects will be identified in the study under a study-specific code. Should results of this study be published, subjects will not be identified through their name or personal information. All research records will be stored in a locked cabinet at all times. Computers used to store electronic data information, are password-protected and only accessible by study staff.

For the maternal questionnaire, no protected health information will be collected from the mothers that complete this form. We will instead indicate the infant's subject ID on the form to correlate the mother's responses with the data collected on their infant for this study.

17. POTENTIAL BENEFITS

Subjects may or not receive benefit from this research study. However, the information we obtain from this study may help us to treat patients with ROP more effectively in the future.

18. RISK/BENEFIT RATIO

The risks of this study as listed above are more than minimal, however, the benefit (to medical science and future patient care) to risk ratio may be large and is in favor of performing the study.

19. EXPENSE TO PARTICIPANT

None. Subjects will not be responsible to cover the costs of the study drug, omega-3 fatty acids. The study doctor will be responsible for all cost of the study drug.

20. COMPENSATION FOR PARTICIPATION

Parents nor subjects will not be paid for their participation in this study.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Shira Robbins, M.D., has the necessary privileges, certification, and licenses to perform the duties outlined in this research plan at UCSD. Dr. Robbins is an employee of UCSD and is supported by grant funding for her time and effort. Dr. Christian Metallo, PhD from the Dept of BioEngineering, will perform laboratory lipid analysis. Courtney Green, MS Dept of BioEngineering, will perform testing on lipid samples. Todd May, MS is a program manager with the Clinical and Translational Research Institute and is a co-investigator.

Louise Laurent M.D. Ph. D is a co-investigator from the UCSD Department of Obstetrics and Gynecology. Vy Ha Tran is a research associate and co-investigator from the UCSD Department of Obstetrics and Gynecology. Radha Ayyagari, Ph.D and Rohan Verma, M.D. are co-investigators, both from the UCSD Department of

Ophthalmology. Dr Ayyagari's lab will provide some of the RNA isolation and analysis. Jennifer Bu is a medical student at UCSD and a co-investigator with the necessary privileges and certificates.

The investigational drug office pharmacists at UCSD MC Hillcrest have all the necessary privileges, certifications, and licenses to perform the duties outlined in the research plan. The neonatal intensive care unit pharmacists and the investigational drug pharmacists will be responsible for administering the total parenteral nutrition to all enrolled infants in the study. The nutrition plan has been discussed in detail with Jacqueline Keller, the UCSD MC Hillcrest NICU principal dietician.

Jessica Yu is a staff research associate at UCSD and has the necessary privileges and certificates. She will help consent and recruit subjects for this study.

Nancy Tang is a clinical nurse and is a co-investigator from the UCSD Department of Pediatrics. She will assist with patient recruitment, obtaining consent, study protocol procedures, sample processing, and data collection. Sarah Lazar, MPH is the Clinical Research Manager for the Division of Neonatology. Along with Sabrina Fossi and Melanie Crabtree, Sarah Lazar will be assisting with patient recruitment, obtaining consent, study protocol procedures, sample processing, and data collection, as well as regulatory assistance coordination on this project.

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23. FUNDING SUPPORT FOR THIS STUDY

The Hartwell Foundation Grant is going to fund this study and provide support for the PI and the sub PIs. An UCSD Academic Senate Grant is also funding clinical coordination of this study.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not Applicable

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Omegaven has been approved by the FDA for use in children and infants with parenteral nutrition associated liver disease (PNALD). In this study we intend to use Omegaven under an IND exemption to study the use of the drug in reducing the incidence and severity of retinopathy of prematurity (ROP). An IND Exemption Supplement form has been provided to the IRB.

26. IMPACT ON STAFF

This study will utilize the neonatology research team to perform all duties in the protocol including performing the procedures/tests for each visit, utilizing EPIC system for reports pertinent to study i.e. lab reports, help with screening, and scheduling appointments. Nursing staff will be responsible for hanging Omegaven infusion with standard of care TPN or hyperal per physician orders.

27. CONFLICT OF INTEREST

There is no financial relationship between any of the investigators on the project. This includes no relationship involving consulting, participation in speakers, bureaus, stock or stock option ownership, or service on advisory boards or the board of directors of a company, or service as a company officer.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not Applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not Applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not Applicable