Study Protocol and Statistical Analysis Plan for NCT03750968

Lutein & Zeaxanthin in Pregnancy – Carotenoid Supplementation during Pregnancy: Ocular and Systemic Effects

The following pages contain the IRB approved study protocol and statistical analysis plan at the most recent renewal approved on 21 December 2022.

Date: Tuesday, May 2, 2023 2:01:03 PM Print Close

IRB_00116610 **Created:** 10/1/2018 12:13 PM

PI: Paul Bernstein M.D. **Submitted:** 11/21/2018

Title: Lutein & Zeaxanthin in Pregnancy (L-ZIP) - Carotenoid Supplementation During Pregnancy: Ocular and Systemic Effects

1. Study Introduction

1. **Responsible Investigator:**
   Paul Bernstein

Email	Training	CoI Date
paul.bernstein@hsc.utah.edu	7/27/2021 MCG	4/3/2023

a. **Position of the Investigator:**

- (●) **Faculty or** Non-Academic Equivalent
- ( ) Student
- ( ) Staff
- ( ) Resident/Fellow
- ( ) Other

2. **Contact Persons for the Responsible Investigator:**

Name	Email	Training
Susan Allman	susan.allman@hsc.utah.edu	1/30/2023 MCG
Melanie Fiuza	melanie.fiuza@hsc.utah.edu	CG
Deborah Harrison	deborah.harrison@hsc.utah.edu	1/31/2023 MCG
Elizabeth Nuttall	Elizabeth.Nuttall@hsc.utah.edu	1/4/2023 MCG
Katie Rogers	katie.rogers@utah.edu	6/17/2022 MCG

3. **Guests of the Responsible Investigator:**

Last Name	First Name	E-Mail

There are no items to display

4. **What type of application is being submitted?**
   New Study Application (or Amendment/Continuing Review)

5. **Title Of Study:**
   Lutein & Zeaxanthin in Pregnancy (L-ZIP) - Carotenoid Supplementation During Pregnancy: Ocular and Systemic Effects

6. **Study Purposes and Objectives:**

The primary objective of this study is to characterize the carotenoid status of mothers during pregnancy, specifically to determine if prenatal supplementation counteracts maternal systemic and ocular carotenoid depletion.

The primary outcome measure will be change in carotenoid levels from enrollment to final study visit (birth of child) as measured in serum, skin and the macula by high-performance liquid chromatography (HPLC), resonance Raman spectroscopy, and macular pigment imaging, respectively.

7. **Is this a multi-site study, where more than one site needs IRB approval?**

○ Yes ● **No**

8. **Background and Introduction:**

The human macula has a high concentration of the dietary carotenoids lutein and zeaxanthin which results in a yellow spot centered on the fovea, the *macula lutea.* Carotenoids are abundant in plants, fruits, and vegetables, and they are thought to play important roles in the physiologic function of the retina and other tissues (Scott et al., 1996; Scarmo et al., 2010; Zimmer et al., 2007; Bernstein et al., 2016). Of the hundreds of carotenoids found in nature, 10 to 15 are detectable in human serum, but only lutein, zeaxanthin, and their metabolites are present in the retina (Bone et al., 1985; Khachik et al., 1997). The potential antioxidant and photoprotective effects of carotenoids, especially with regard to age-related macular degeneration (AMD), have been studied extensively in the laboratory and in clinical studies (Seddon et al., 1994; Bernstein et al., 2002; Eye Disease Case-Control Study Group, 1993), and recent reports have demonstrated a role of dietary and supplemental carotenoids in slowing or preventing AMD (Age-Related Eye Disease Study (AREDS) Report No. 22, 2007; AREDS2 Report No. 3, 2014).

Studies also suggest a functional role for the macular carotenoid pigment earlier in life, at a time when they may enhance contrast sensitivity, decrease glare disability, and even increase visual acuity (Kvansakul et al., 2006; Stringham et al., 2008; Olmedilla et al., 2003). The physiological accumulation of the macular carotenoid pigments occurs even *in utero* (Malone, 1975; Dimenstein et al., 1996). Investigators have recently shown that the macular pigment is detectable immediately after birth, correlates with infant and maternal serum zeaxanthin levels, and progressively increases through the first seven years of life (Bernstein et al, 2013). This suggests that the macular carotenoids play physiological and protective roles throughout the lifecycle and may be particularly important during infant visual development.

Prenatal vitamin and micronutrient supplementation is standard-of-care for pregnant women worldwide; however, with the exception of a few ingredients, most prenatal supplementation guidelines are not yet supported by substantial prospective clinical research. Recently, prenatal supplements with added lutein and zeaxanthin have entered the American market with the stated intentions of enhancing infant visual and neural development and maintaining maternal health. Although clinical trials were never performed to support these contentions, it is physiologically plausible from the neonate's perspective because these dietary carotenoids are selectively concentrated in human ocular and neural tissue *in utero*, especially during the third trimester of pregnancy.

From the mother's perspective, the last trimester of pregnancy is a time when she must transfer some of her carotenoid stores to the developing infant via the placenta, potentially putting her at risk for depletion systemically and in her ocular tissues. On review of the published literature, there are conflicting data regarding systemic maternal carotenoid status throughout pregnancy, and absolutely nothing is known about maternal macular pigment levels in the eye during pregnancy. Some, but not all, studies report lower serum carotenoid levels in pregnant women. Bernstein and others (Henriksen et al., 2013; Kiely et al., 1999; Zhang et al., 2001) have reported that mothers who did not take lutein or zeaxanthin supplements during pregnancy had >50% reductions of serum lutein and zeaxanthin concentrations and ~20% lower total skin carotenoids at the time of delivery when compared to our clinic's average of unsupplemented non-pregnant adults.

Prospective, controlled clinical trials to demonstrate the benefits of carotenoid supplementation during pregnancy have never been conducted. To obtain data relative to the feasibility of such trials, this study will be a comprehensive, prospective assessment of prenatal lutein + zeaxanthin supplementation on maternal and infant ocular and systemic biomarkers of carotenoid status throughout pregnancy.

Please see pp. 27- 30 of the protocol for the list of literature cited.

2. Study Location and Sponsors

1. **Add all locations applying for approval of research via the University of Utah IRB or Human Research Protection Program (HRPP).**

   Click the appropriate button(s) below to add locations:

	Site Name	Investigators Name	Covered Entity	Sub Sites
View	University of Utah	Paul Bernstein	Yes	

2. **Will a Central IRB (CIRB) or Single IRB (SIRB) model be used for review of this study for the sites listed in this application?**
   ○ Yes ● **No**

3. **Indicate the source(s) of funding obtained or applied for to support this study.**

	Sponsor	Sponsor Type	Sponsor Contact Information	Prime Sponsor	Prime Sponsor Type	OrgID
View	DHHS NATIONAL INSTITUTES OF HEALTH	Federal Government				10154
View	HEIDELBERG ENGINEERING GMBH	Industry	Heidelberg Engineering GmbH Max-Jarecki-Straβe 8 69115 Heidelberg Germany www.HeidelbergEngineering.com			00017492

4. **Does this study have functions assigned to a Contract Research Organization (CRO)?**
   ○ Yes ● **No**

5. **Does this study involve use of the Utah Resource for Genetic and Epidemiologic Research (RGE)?**
   Examples: Utah Population Database (UPDB), Utah Cancer Registry (UCR), All Payers Claims Database (APCD), etc.
   ○ Yes ● **No**

Title: Lutein & Zeaxanthin in Pregnancy (L-ZIP) - Carotenoid Supplementation During Pregnancy: Ocular and Systemic Effects

Addition of a Site

1. **Site Name:**
   University of Utah

2. **Site Principal Investigator**
   ☑ **Mark if Same as Responsible Investigator (syncs with investigator on the first page)**
   Paul Bernstein

Email	Training	CoI Date
paul.bernstein@hsc.utah.edu	7/27/2021 MCG	4/3/2023

   a. **Position of the Site Principal Investigator**
   Faculty or Non-Academic Equivalent

   b. **Will the Site PI consent participants?** ○ Yes ● **No**

3. **Site Contact Persons, if different from the Site PI:**
   ☑ **Mark if Same as Contacts for Responsible Investigator (syncs with contacts on the first page)**

Name	Email	Training
Susan Allman	susan.allman@hsc.utah.edu	1/30/2023 MCG
Melanie Fiuza	melanie.fiuza@hsc.utah.edu	CG
Deborah Harrison	deborah.harrison@hsc.utah.edu	1/31/2023 MCG
Elizabeth Nuttall	Elizabeth.Nuttall@hsc.utah.edu	1/4/2023 MCG
Katie Rogers	katie.rogers@utah.edu	6/17/2022 MCG

4. **Site Staff and Sub-Investigators**

Name	Email	Training	Obtaining Consent	CoI Date
Emmanuel Kofi Addo	u1272149@utah.edu	9/13/2022 MG	☐	5/2/2023
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Melanie Fiuza	melanie.fiuza@hsc.utah.edu	CG	☑	2/2/2022

Name	Email	Training	Obtaining Consent	Col Date
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Kelly Vorwaller	kelly.vorwaller@hsc.utah.edu	3/7/2023 MCG	☑	11/14/2022
Joseph Worden	joseph.worden@hsc.utah.edu	5/13/2021 MCG	☐	12/5/2022

5. **Site Guests:**

Name	Email	Training
Kathryn Szczotka	kathryn.szczotka@hsc.utah.edu	4/28/2021 MCG

6. **Select HIPAA coverage for this study:**
Study procedures will be conducted within a HIPAA Covered Entity at this site (HIPAA Privacy Rule applies)

7. **Select the study procedures that will be conducted at this site:**

Recruitment
Consent/Enrollment

Research observation/intervention with participants

Data collection

Data analysis

Do you have an enrollment goal or anticipated enrollment number for this site?

- (●) **Yes**
- ( ) No

Enrollment Number:
60 mothers and 60 infants

8. **Select the University of Utah department responsible for this research:**
   OPHTHALMOLOGY-CLINICAL STUDIES

9. **Add any additional sites that are part of this performance group**
   There are no items to display

Sponsor Information

a. Are you receiving award or contract management for the sponsored funds through the University of Utah Office of Sponsored Projects?

● **Yes** ○ No

If yes, select the associated OSP Proposal ID/DSS through eAward to link it to the ERICA system.

You must have a fully approved Proposal ID/DSS number through eProposal which will show up in eAward after OSP has integrated the ID. To access the eAward application, use the instructions on the OSP website.

Link to a Proposal ID/DSS through eAward

Proposal ID/DSS: 10046346
PI: BERNSTEIN,PAUL S
Sponsor: DHHS NATIONAL INSTITUTES OF HEALTH
Prime Sponsor:
Department:
Short Title: CAROTENOID SUPP DUR PREGNANCY
Sponsor Award Number:
Type: Federal Government
Award Start Date: 4/1/2018
Award End Date: 3/31/2020
Prime Sponsor Type:

Sponsor Information

a. Are you receiving award or contract management for the sponsored funds through the University of Utah Office of Sponsored Projects?

○ Yes ● **No**

If no, indicate how the funds are being received:
Other

If 'Other', please explain how funds are being received:
Heidelberg has provided Dr. Bernstein with a beta version of the macular pigment imaging software at no cost. It must be used under IRB approval as it is not yet FDA approved.

Heidielberg will not be receiving data from this study and has no interest in the conduct of the study.

Sponsor:
HEIDELBERG ENGINEERING GMBH

Previously, the following data was entered on your IRB application:

Sponsor Contact Information:
Heidelberg Engineering GmbH
Max-Jarecki-Straβe 8
69115 Heidelberg
Germany
www.HeidelbergEngineering.com

3. Participants

1. Ages of Participants:

Less than 7 years old	(Parental permission form needed)
18 and older	(Consent form needed)

2. Specific age range of participants (e.g., 7-12 years old, 60+, etc.):
Pregnant women 18 or older and their infants

3. Indicate any vulnerable participant groups (other than children) included:

Pregnant women and fetuses (CFR Part 46, Subpart B)

If "Other", please specify:

If "None" and no children are involved, answer the following question.
Has the participant selection process overprotected potential subjects who are considered vulnerable so that they are denied opportunities to participate in research?
◯ Yes ◯ No

4. Number of participants to be included and/or enrolled in this entire study, across all study locations: 60 mothers and 60 infants

At Utah prior to October 2019: 60 mothers and 60 infants

5. Characteristics of Participants/Inclusion Criteria:

Pregnant women, 18 or older of all races and ethnicities who:

- have an uncomplicated obstetric history
- plan to deliver either vaginally or by Caesarian section at the University of Utah for their current pregnancy

6. Participant Exclusion Criteria:

Women will be excluded if they:

- Have regularly taken carotenoid supplements containing more than 0.5 mg of lutein and/or zeaxanthin daily during the past six months.
- Have significant eye disease associated with macular pigment abnormalities such as Stargardt disease, albinism, or macular telangiectasia type II (MacTel).
- Have any conditions associated with high-risk pregnancies such as adolescent pregnancy, multiparity, current or past history of diabetes, pre-eclampsia, previous premature delivery, drug abuse, or other significant medical illness.

7. **Is a substantial percentage of the participant population anticipated to be non-English speaking?**

● **Yes** ○ No

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Vulnerable Populations

Justification Requirements for the Inclusion of Vulnerable Populations

1. **How does the nature of the research require or justify using the proposed subject population?**
   The main objectives of the study are to describe mothers' carotenoid status during pregnancy, and the relation between maternal nutritional status and its effect on the newborn.
2. **Would it be possible to conduct the study with other, less vulnerable subjects?**
   ○ Yes ● **No**

   If yes, justify the inclusion of vulnerable subjects:
3. **Is this population being included primarily for the convenience of the researcher?**
   ○ Yes ● **No**

   If yes, explain:

4. Study Information

1. **Design of Study (select all that apply):**

   ☐ **Non-Experimental and/or Descriptive Research Design:**

   There are no items to display

   ☑ **Experimental and/or Interventional Research Design:**

   Blinded Trial (Single or Double Blinded)
   Randomized Trial
   Phase II Clinical Trial

   ☐ **Development of a research resource (repositories, databases, etc.)**

   There are no items to display

   ☐ **Other**

2. **Does your study involve the use of any placebo?**
   ○ Yes ● **No**

3. **Length of entire study, from initiation through closeout:**
   2 years

4. **How will participants be recruited or identified for inclusion in the study?**

   a. **Select all methods that will be used:**

   In-person contact (e.g., patients, students, etc.)

   Written or electronic record review

   Written advertising (flyers, brochures, website postings, newspaper ads, etc.)

   b. **Describe the recruitment/participant identification process in detail (e.g. who will review charts or records, who can refer participants to the study, where will flyers be posted, how often will recruitment letters be sent, when will follow-up phone calls be made, etc.):**

   Mothers who are eligible for the study will be recruited from the OB/GYN Clinics of the University of Utah during a first trimester prenatal visit (prior to week 13), with agreement from their attending Obstetrician.

   Recruitment brochures will be posted in clinic areas.

   A web-based tool, the Human Subjects Recruitment Tool (HSRT), will be used to screen for potential patients who meet the IRB approved eligibility requirements **and** have a clinic appointment/inpatient visit at one of the approved clinic and/or inpatient locations.

   We will also screen patient appointment logs through a Waiver of Authorization to identify potential patients who meet initial eligibility criteria.

   Potential participants will then be approached about the study during one of their prenatal clinic visits. Study personnel will describe the study in detail and review the study protocol with the patient.

Data from the Human Subjects Recruitment Tool (HSRT) will become unavailable the day the IRB expires or when the research team notifies the EDW that the recruitment period closes.

5. How will consent be obtained?

Informed Consent Process (with or without a document)

6. Describe all the procedures chronologically, from screening/enrollment through study closeout, which will be completed in the research project.

Study Visit Schedule

Initial evaluation of each mother's carotenoid status will be obtained prior to starting any study supplements. Subsequent evaluations while participants are taking the study supplements will be performed in conjunction with routine prenatal visits to their Obstetrician, at approximately 22-26 weeks gestational age and again at 37-39 weeks gestational age. All mothers will undergo a final assessment within two weeks of giving birth.

Infants' evaluations will be performed in the first two weeks of life, either during the original hospital stay or at a follow up outpatient clinic visit.

	Screening/ Baseline	**Maternal Supplementation**		
Visit:	**T1**	**T2**	**T3**	**Birth**
Timeframe:	Before 14 Wks GA	22-26 Wks GA	37-39 Wks GA	0 to 2 Wks
Informed Consent	X			
Randomization	X			
Maternal visual acuity and contrast sensitivity	X	X	X	X
Maternal nutritional surveys	X	X	X	X
Dilated eye examination	X			
Maternal serum carotenoids	X	X	X	X
Maternal macular pigment imaging	X	X	X	X
Maternal skin carotenoids	X	X	X	X
Dispense prenatal supplement and do pill counts	X	X	X	X
Infant cord blood carotenoids				X
Infant macular pigment imaging				X
Infant foveal imaging (sdOCT)				X
Infant skin carotenoids				X

Unscheduled Visits

Mothers may be seen for Unscheduled Visits if deemed necessary for repeat measurements or follow-up of Adverse Events. If a mother delivers her baby prematurely, she and her infant will remain in the study and will be asked to complete the final study visit.

Description of Study Assessments:

Visual Function - Manifest refraction, and measurement of best-corrected visual acuity and contrast sensitivity of the mothers will be obtained by certified ophthalmic technicians using standardized protocols. The study staff performing visual acuity will be masked to the treatment assignment. Best-corrected visual acuity testing will be assessed on ETDRS back-lit charts starting at a distance of 4 m, and should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Contrast sensitivity will be measured by the Pelli-Robson threshold contrast sensitivity chart at 1 m.

Maternal Eye Exam - The complete ophthalmic exam will consist of the following:

- External examination of the eye and adnexa.
- Routine screening for eyelids/pupil responsiveness (including ptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light and afferent pupillary defect).
- Slit-lamp examination [cornea, anterior chamber, iris, lens, aqueous reaction (cells and flare).
- Dilated fundus exam of the study eye including evaluation of retina and vitreous (i.e. posterior segment abnormalities, retinal hemorrhage/detachment, and vitreal hemorrhage density and vitreous cells).
- IOP measurement - A measurement of intraocular pressure will be conducted using a Tono-pen tonometer. This should be performed prior to dilating the eyes and the same method should be used for all measurements in the same subject throughout the study.

Skin Carotenoid Levels - A high-sensitivity scanner (Raman device) suitable for measurements of infants and adults will be used for this study. The measurements are taken by placing a probe on the subject's palm of the hand (adults) or sole of the foot (infants) with a special light source that does not generate heat and is harmless to one's vision as long as it is not viewed directly for a long time (similar in risk to a laser pointer). The measurements require 30 seconds of skin contact and another 30 seconds to obtain the reading. The measurement is repeated 3 times to confirm the accuracy, so a total of 3 minutes of assessment is needed.

Infant Macular Pigment Measurements - Infant macular measurements will be performed using blue light reflectometry. The infant's pupils will be dilated with Cyclomydril drops (standard-of-care for dilated eye examinations of newborns), and then the swaddled baby's eyes will be opened with a pediatric lid speculum. Posterior pole 80-degree images centered on the fovea will be taken with a retinal camera by a certified ophthalmic photographer under the supervision of a Pediatric Ophthalmologist using its optional blue light source and deliberately omitting the fluorescein angiography barrier filter in the collection light path. Color images will also be taken to facilitate identification of key retinal landmarks. Total image acquisition time is just a few minutes.

Infant Foveal Anatomy - The sdOCT (Bioptigen) is an FDA-approved handheld portable unit that is used to image the foveal anatomy of premature and full-term infants. Swaddled infants will have their eyelids gently opened by the certified ophthalmic photographer or a Pediatric Ophthalmologist. Vertical and horizontal scans will then be acquired. The OCT images will be obtained prior to the contact images with the retinal camera.

Maternal Macular Pigment Levels - Mothers' macular pigment will be measured using the dual wavelength autofluorescence method which measures attenuation of lipofuscin autofluorescence by blue absorbing macular pigment. The subject looks at a fixation target with her dilated study eye for about 30 seconds as her macula is scanned sequentially with alternating 486 nm (blue) and 518 nm (green) lasers, and autofluorescence images are collected. Macular pigment images are prepared by digitally subtracting the green image from the blue image using appropriate correction factors to compensate for the absorption spectrum of the macular carotenoid pigment and then analyzed using macular pigment analysis software after setting the zero point at 9 degrees of eccentricity. This instrument and software has proven to be highly reliable and reproducible, especially when measuring macular pigment volume under the curve at 9 degrees.

Serum Carotenoid Levels - Blood samples obtained from mothers and from infant cord blood will be analyzed for serum carotenoid content using well-established laboratory protocols that can provide baseline separations of all common dietary carotenoids. Whenever possible blood samples will be obtained by piggy backing onto a routine clinical blood collection.

Dietary Questionnaires - At each study visit mothers will be asked to complete the LZQ quantitative food frequency questionnaire that captures ~90% of the lutein/zeaxanthin foods consumed in the US, based on National Health and Nutrition Examination Survey data.

Safety Evaluations - Any clinically significant abnormalities persisting at the end of the study/ early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study includes procedures to monitor safety, including complete Ophthalmic exams and monitoring of adverse events.

Optional Specimen Collection and Banking Sub-Study

Participants will be asked to allow a sample of placenta tissue to be collected and stored for future research related to maternal to infant carotenoid transport on a tissue level.

Participants will be asked to provide a saliva sample to be stored and used for future research related to the genetics of carotenoid metabolism enzymes.

Participants will be asked to allow a portion of their blood collected at study visits to be stored for future research related to the genetics of carotenoid metabolism.

Participation in these procedures is optional and participants may decline any or all of them and still participate in the main study. Participant identifiers will be stored separately from the banked samples and participants will be able to withdraw their samples if they so desire.

Banked samples may be shared with other researchers, who must have IRB approval for their use and material/data transfer agreements with the University of Utah as applicable.

7. **Are all procedures for research purposes only (non-standard or non-standard of care procedures)?**

○ Yes ● **No**

If no, list the procedures that are performed for research purposes only (non-standard or non-standard of care procedures):

All Protocol-specified procedures are for research purposes only, with the exception of dispensing prenatal supplements. Expectant mothers will be taking prenatal supplements whether or not they agree to participate in this study.

8. **Is there a safety monitoring plan for this study?**

○ Yes ● **No**

9. **Provide a summary of the statistical methods, data analysis, or data interpretation planned for this study. Factors for determining the proposed sample size (e.g., power) should be stated.**

Statistical Analysis

The study outcome data will be analyzed by a consultant from the University of Utah Study Design and Biostatistics Center of the Center for Clinical and Translational Science.

Image analysis of retinal camera macular pigment measures will be conducted in Dr. Bernstein's laboratory. Foveal anatomy parameters such as width, depth, and layer structure will be assessed by Drs. Hartnett and Bernstein using methods based on previously published protocols.

Sample Size Calculation and Power Considerations

Statistical power and sample size (*N*) for one of the primary outcome measures, maternal skin carotenoids at birth, was determined using data from the previous study by Henriksen et al. (2013) in which the average maternal skin carotenoids ± SD at birth was 34000 ± 8300. This value is 20% lower than the University of Utah Moran Eye Center clinic average value of ~42,500 Raman counts reported for the ancillary AREDS2 study (Bernstein et al., 2012). With power of 0.90 and alpha 0.05, a sample size of 20 was calculated for each group in order to detect and prevent a 20% decline during pregnancy. In order to accommodate subsequent ineligibility due to premature birth, low birth weight, or other problems (~10%) and to plan for expected noncompliance and loss to follow up (~20%), we intend to enroll 30 subjects in the Carotenoid Supplementation Group and another 30 in the Control Group.

The other outcome measures (maternal ocular carotenoid depletion during pregnancy, infant carotenoid status at birth, and the exploratory outcome measures of foveal maturity at birth and visual function changes during pregnancy) are not as well characterized, but we estimate that a similar sample size of 20 patients per group will be sufficient to detect differences in these indices.

Statistical Analysis Sets

The Intent-to-Treat set will include all randomized subjects who complete the Baseline Visit carotenoid status evaluations and receive study supplements. Subjects will be analyzed by the supplement arm assigned at the Baseline Visit.

A modified Intent-to-Treat set will include all randomized subjects who receive investigational product and complete carotenoid evaluations for at least one trimester study visit while utilizing study supplements.

Efficacy Analyses

The primary, secondary and exploratory efficacy analyses will be performed using the modified Intent-to-Treat subject set. Paired t-tests will compare the carotenoid status at enrollment and at the final study visit of the mothers receiving carotenoid supplementation to mothers not receiving carotenoid supplementation. We will also compare carotenoid status of infants whose mothers received carotenoid supplementation to infants of mothers without carotenoid supplementation. Significance will be set at 2-tailed $P<0.05$. The associations between maternal and infant carotenoid status will be assessed with regression analysis.

Subgroup analyses will be performed to assess the influences of maternal dietary carotenoid intake, compliance with study supplement use, co-existing medical conditions, BMI, infant gender, and other factors on our study results, with proper attention to the effects of multiple tests on the ability to draw conclusions.

The complete statistical analysis plan will be finalized prior to database lock, and will provide statistical methods as well as descriptions of how missing, unused and spurious data will be addressed. Summarization of study data will be prepared of subject demographics, baseline characteristics, and investigational product exposure.

Safety Analyses

Serious and unexpected adverse events will be collected from the time of the first study supplement administration until a subject completes the study or discontinues prematurely. Treatment emergent adverse events (TEAEs) are defined as those AEs that develop or worsen after the first dose of study supplement and up to 30 days beyond the last dose of study medication. The current version of MedDRA will be used to classify all AEs.

Treatment- emergent adverse events will be summarized by System Organ Class and Preferred Term, in accordance with the MedDRA coding dictionary. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as related to study treatment by the Principal Investigator. The number of subjects reporting SAEs will also be tabulated. Adverse event summaries will be presented for each treatment group separately.

Adverse events will be summarized by MedDRA coding terms, and separate tabulations also will be produced for related adverse events (those considered by the Investigator as definitively drug related), serious adverse events and discontinuations due to adverse events. Findings from ophthalmologic examinations will be tabulated for changes over time on study. Separate summaries will be prepared for systemic (non-ocular) and ocular AEs, with events in the study eye and non-study eye summarized separately.

Consent Process

1. **The following investigators and internal staff will obtain consent (as indicated on the Study Location and Sponsors Page):**

Susan Allman	University of Utah
Melanie Fiuza	University of Utah
Kelliann Ordonez	University of Utah
Emily Powers	University of Utah
Kelly Vorwaller	University of Utah

List by name, role, and affiliation any others who will obtain consent (e.g. Dr. John Smith, Co-Investigator, etc.).

2. **Describe the location(s) where consent will be obtained.**
Consent will be obtained in private research offices or clinic rooms

3. **Describe the consent process(es), including the timing of consent. Describe whether there is a waiting period between the consent process and obtaining consent from the participant (i.e., any time between informing participants and actually obtaining consent).**
If a patient appears to meet the criteria for the trial, she will be told about the study and asked for written informed consent to participate in the trial.

If they wish to consider whether or not they want to participate in the study, they may have time to think about the study and provide consent as long as there is enough time between approach and the gestational age required for eligibility.

4. **Describe what measures will be taken to minimize the possibility of coercion or undue influence.**
Research staff that conduct this consent process have been participating in research for several years. They are experienced with obstetric study populations and will spend the time required to answer any questions or concerns. If there appear to be concerns, the woman will be encouraged to take time to think about the study.

No additional benefits other than those described in the consent document will be discussed.

5. **Describe the provisions that are made to allow adequate time to exchange information and questions between the investigator and participant.**
The research staff are experienced in interviewing and working with the obstetric population. They will be certain to take the time needed to ensure that the person understands the study and is consenting willingly. If the woman continues to have questions, she will also be offered the opportunity to discuss the study in further detail with the PI. She will also be given the opportunity to return at a later time if she needs more to make a decision.

6. **Will a legally authorized representative (LAR) be used?**
○ Yes ● **No**

7. **Will a language other than English be used to obtain consent?**
● **Yes** ○ No

   a. **Please indicate which form will be used:**
   A translated short form with an English long form.

Please provide justification for why a full, translated consent document will not be used:
After the first patient is consented with the short forms, we will get the full consent form translated into the patient's native language and provide a translation certificate. The consent will then be submitted to the IRB via an amendment application and the first patient will be re-consented with the fully translated ICF. Any future patients would be enrolled with a fully translated ICF as long as it is maintained, or a short form again will be used, and an immediate translation will take place. An interpreter will explain the clinical trial and communicate with the patient about their potential participation. Professional translation services will be provided. It will be documented that the patient demonstrated an understanding of the study. The interpreter will sign and date the consent.

b. **Describe whether translation services will be used for the consent process and how the consent process will be conducted?**
In the event that a participant does not speak English, the oral presentation will be translated with the use of an interpreter. The written summary of the oral presentation will be the IRB approved long consent document. Hospital-based, professional translation services will be provided to all non-English speaking study participants. Consent will be documented using a short form. A third-party witness/interpreter will be present during the oral presentation and will sign both the long form and the short form, the interpreter can act as the witness. They will be fluent in both English and the patient's native language. The person obtaining consent will sign the long form. The participant will sign the short form. The participant will receive a copy of the consent form in English and the short form.

8. **Are you requesting that documentation of informed consent be waived by the IRB (a consent process in place, but no documentation of consent, e.g. questionnaire cover letter, web-based consent, consent without signature, etc.)?**
○ Yes ● **No**

If yes, complete the following:

a. **Explain why the waiver of consent documentation is being requested.**

b. **Justification for the waiver is one of the following:**
There are no items to display

5. Data Monitoring Plan

1. **Privacy Protections:** Privacy refers to persons and to their interest in controlling access of others to themselves. Privacy can be defined in terms of having control over the extent, timing and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. **What precautions will be used to ensure subject privacy is protected?**

Select all that apply:

The research intervention is conducted in a private place

Discussing the study with participants individually instead of in front of a group

Other or additional details (specify):
In order to maintain subject privacy, study personnel will not discuss genetic testing with the participant unless they are in a private area.

2. **Confidentiality Precautions:** Confidentiality is an extension of the concept of privacy; it refers to the subject's understanding of, and agreement to, the ways identifiable information will be stored and shared. Identifiable information can be printed information, electronic information or visual information such as photographs. **What precautions will be used to maintain the confidentiality of identifiable information?**

Select all that apply:

Storing research data on password protected computers or in locked cabinets or offices

Other or additional details (specify):
Genetic testing results will not be shared with participants or included in their medical record.

3. **Will photos, audio recordings, or video recordings, or medical images of participants be made during the study?**

● **Yes** ○ No

If yes, describe the recording/images and what will become of them after creation (e.g., shown at scientific meetings, stored in the medical/research record, transcribed, erased, etc.):
Ophthalmic images will be stored in the research record and in the electronic medical record.

4. **How will study data and documentation be monitored throughout the study?**

Select all that apply:

Periodic review and confirmation of participant eligibility

Periodic review of informed consent documentation

Periodic review of the transfer/transcription of data from the original source to the research record

Confirmation that all appropriate information has been reported to the sponsor, oversight agencies (such as the FDA), and/or IRB

Other additional details (specify):

5. **Who will be the primary monitor of the study data and documentation?**

Select all that apply:

Study Coordinator or Research Nurse

Data (and safety) Monitoring Board or Committee

Other or additional details (specify):

6. **How often is study data and documentation monitoring planned (e.g., monthly, twice a year, annually, after N participants are enrolled, etc.)?**
   Data monitoring will occur every 3 months.

6. Risks and Benefits

1. Describe the reasonable foreseeable risks or discomforts to the participants:

Risks of Carotenoid and Control Supplements – Both kinds of supplements are within the standard of care expectant mothers would receive if they were not in the study. They pose no additional risk to participants.

Risks of Visual acuity and contrast sensitivity – These are routine vision tests and pose no risk to participants above standard medical care.

Risks of Ophthalmic imaging – Light levels projected on the retina during the photographs and macular pigment measurements are well within established safety limits. Participants may notice a central dark spot in their vision similar to the afterimage generated by a camera flash. This will fade in about 5 minutes. Infants may experience discomfort during the macular pigment imaging and foveal imaging. Parents may feel emotional distress when observing the infant undergoing this safe examination.

Risks of Carotenoid skin measurements – There are no expected risks from the light exposure from the skin measurement. It is important not to look directly at the laser for a long period of time.

Risks of Blood draws – Whenever possible the blood samples for this study will be taken at the same time participants are having blood drawn for routine prenatal blood work. The blood sample from the infants umbilical cord will be taken at the same time blood is collected for his/her routine care.

Risks of Eye exams – The dilation drops used for the exams are considered standard of care for dilated eye exams during pregnancy.

Risks of Nutrition surveys and supplement logs – recording diet and supplement intake will take a few minutes of participants time, but poses no risk.

Risks of genetic research and sample banking - There is a potential risk of loss of confidentiality, but procedures are in place to make this highly unlikely.

Unforeseeable Risks - In addition to the risks listed above, participants may experience a previously unknown risk of side effect.

2. Describe the potential benefits to society AND to participants (do not include compensation):

Participants may not directly benefit from participating in this study. Participants may receive nutritional benefits from taking the supplements. We hope the information we learn from this study will help us provide better care for pregnant mothers and their infants in the future.

3. Are there any costs to the participants from participation in research?

○ Yes ● **No**

If yes, specify:

4. Is there any compensation to the participants?

● **Yes** ○ No

a. **If yes, answer the following:**
Specify overall amount:
$125.00

b. **Specify when participants will be paid (e.g. at each visit, at end of study, etc.):**
At each study visit.

c. **If applicable, please specify payment by visit or other time interval (e.g. $10 per visit, etc.):**
$25.00 for the first 3 study visits. $50 for the final study visit.

d. **If applicable, explain plan for prorating payments if participant does not complete the study:**
Participants will be paid for each study visit they complete.

7. HIPAA and the Covered Entity

1. **Does this study involve Protected Health Information (PHI) or de-identified health information?**
   ● **Yes** ○ No

   a. **Select the method(s) of authorization that will be used:**

   (Consent and) Authorization Document

   Waiver or Alteration of Authorization

   De-identified

   Select the method of de-identification: Safe Harbor De-Identification

   b. **Will PHI be disclosed outside the Covered Entity?**
   ● **Yes** ○ No

   To whom?
   The NEI and the FDA

   And for what purposes?
   For oversight of the study

Does this study involve any of the following:

2. **The investigational use of a drug?**
   ● **Yes** ○ No

3. **The investigational use of a medical device?**
   ● **Yes** ○ No

4. **Is this an investigator-initiated drug or device trial lead by the Principal Investigator?**
   ● **Yes** ○ No

5. **Exposure to radioisotopes or ionizing radiation?**
   ○ Yes ● **No**

6. **A Humanitarian Device Exemption (HDE)?**
   ○ Yes ● **No**

7. **Genetic testing and/or analysis of genetic data?**
   ● **Yes** ○ No

8. **Creating or sending data and/or samples to a repository to be saved for future research uses?**

● **Yes** ○ No

9. **Are you:**
   - **Collecting samples of blood, organs or tissues from participants for research purposes;**
   - **Introducing Recombinant or Synthetic Nucleic Acids (e.g. viral vectors, oligonucleotides) or cells containing recombinant nucleic acids (e.g. CAR-T) into participants; OR**
   - **Introducing other biological materials (e.g. bacteria, viruses) into participants.**

   ○ Yes ● **No**

10. **Does this study involve any of the following?**
    - **Cancer Patients**
    - **Cancer Hypothesis**
    - **Cancer risk reduction**
    - **Cancer prevention**

    ○ Yes ● **No**

11. **Any component of the Clinical and Translational Science Institute (CTSI)?**

    ○ Yes ● **No**

    The Clinical Research Center (CRC)?

    ○ Yes ○ No

Request for Waiver or Alteration of Authorization

Request for Waiver of Authorization for Recruitment Only

This option must only be used if you are reviewing PHI in order to identify eligible participants BEFORE approaching them to obtain consent and authorization. All other waiver requests must be entered below.

Waiver of Authorization for Recruitment Requested

Other Requests for Waivers of Authorization:

- *Click "Add" below to add a new waiver request to this application.*
- *Click the waiver name link to edit a waiver that has already been created.*
- *To delete a waiver request, contact the IRB.*

Date Created	Type of Request	Purpose of Waiver Request
There are no items to display		

Request for Waiver or Alteration of Authorization

Request for Waiver of Authorization for Recruitment Only

The PI must agree to the terms of this waiver request as described on this page. When the PI uses the "Submit" activity to submit the application for IRB review, a checkbox to accept the terms will be available in the "Submit" activity window.

This waiver request includes justification for waivers of consent for recruitment only, according to 45 CFR 46.116(d).

Terms for the Waiver of Authorization:

- The purpose of this waiver of authorization is to allow for the use of PHI in order to identify and recruit individuals who may be eligible to participate in the specific research described in this IRB application. The waiver of authorization is necessary to accommodate this minimal-risk research activity prior to seeking a full authorization from research participants.
- Methods for identifying individuals may include the following:
  - Reviewing medical charts
  - Reviewing databases that include PHI
  - Reviewing other medical- or health-based documents that include PHI
- Identifiable information used under this waiver may include the following, as this is the minimum necessary for identifying eligible individuals:
  - Name
  - Contact information, such as phone number, address, or email address
  - An ID number, such as MRN or SSN
  - Date of birth
  - Medical and health information that may determine study eligibility
- Any PHI recorded by the study team will only be used for recruitment and determining study eligibility. After this has been completed, the PHI must be removed from the research record or destroyed, unless the participants have given authorization for continued use of the PHI.
- PHI will only be viewed by approved members of the study team and will not be disclosed for research purposes to any individual or institution without the participants' authorization for such use and disclosure of the PHI.
- PHI will be stored in a secure manner according to HIPAA privacy and security provisions.

IRB_00116610 **Created:** 10/1/2018 12:13 PM

PI: Paul Bernstein M.D.

Submitted: 11/21/2018

Title: Lutein & Zeaxanthin in Pregnancy (L-ZIP) - Carotenoid Supplementation During Pregnancy: Ocular and Systemic Effects

Safe Harbor De-Identification

1. This declaration applies to the following part(s) of this study:

A. ☐ All of the information used or disclosed in this study.

B. ☐ The information received or collected from these sources:

C. ☑ The information shared with or disclosed to these groups: Tufts University, NYU Langone

2. As the principal investigator for this study, I declare the following:

1. To the best of my knowledge, the information could not be used (alone or with other information) to identify an individual who is a subject of the information, and

2. None of the following types of information, regarding subjects or relatives, employers, or household members of subjects, are used or disclosed in the part of this study indicated above:

   a. Names;

   b. All geographic identifiers except state or the first three digits of a zip code (however, all data from the following 17 3-digit zips are combined together under "000": 036, 059, 063, 102, 203, 556, 692, 790, 821, 823, 830, 831, 878, 879, 884, 890, and 893)

   c. The month and day (the year can be kept) from all dates directly related to an individual, including birth date, admission date, discharge date, date of death. Ages over 89 are combined in a single category of "Age 90 and older."

   d. Telephone numbers;

   e. Fax numbers;

   f. Electronic mail addresses;

   g. Social security numbers;

   h. Medical record numbers;

   i. Health plan beneficiary numbers;

   j. Account numbers;

   k. Certificate/license numbers;

   l. Vehicle identifiers and serial numbers, including license plate numbers;

   m. Device identifiers and serial numbers;

   n. Web Universal Resource Locators (URLs);

   o. Internet Protocol (IP) address numbers;

p. Biometric identifiers, including finger and voice prints;

q. Full face photographic images and any comparable images; and,

r. Any other unique identifying number, characteristic, or code, except as permitted for re-identification.

3. If I assign a code or other means of record identification to allow de-identified information to be re-identified,

1. The code or other means of record identification is not derived from or related to information about the individual and is not otherwise capable of being translated so as to identify the individual, and

2. I will not use or disclose the code or other means of record identification for any purpose other than re-identification, and I will not disclose the mechanism for re-identification.

4. Before I allow a code to be used to re-identify this information,

1. If the purpose of the re-identification is within the scope of the original protocol, I will obtain approval of an amendment from the IRB and comply with the requirements of HIPAA; or

2. If the purpose of the re-identification is outside the scope of the original protocol, I will submit a full New Study Application, obtain IRB approval, and comply with the requirements of HIPAA.

Investigational Use of a Drug

#1: Complete this column if an investigational new drug (IND) number is required.

A. Provide IND Number(s):

IND #	Drug name	IND Holder
141801	DHA Softgels	Paul Bernstein, MD, PhD

B. Attach verification of the IND number to the documents and attachments page. Please check the method by which you choose to verify the IND number:

FDA letter (this is the actual letter sent to the holder of the IND with the number)

#2: Complete this column if you believe an IND is not required.

A: Drug name:

B. Select one:

C. Check all of the following that that apply:

There are no items to display

Statement of Compliance

The use of investigational drugs in facilities covered by the University of Utah IRB must follow the policies and procedures of the facility in which the drug(s) will be administered and/or dispensed.

University of Utah Hospitals

If you are conducting inpatient research at the University Health Center or Huntsman Cancer Hospital, please review the Department of Pharmacy Policies and Procedures and contact the appropriate investigational pharmacist listed below.
University of Utah Hospitals & Clinics Investigational Pharmacy: **(801) 585-0272**

Primary Children's Hospital

If you are conducting inpatient or outpatient research at Primary Children's Hospital, please contact the investigational pharmacist at the number listed below:
Primary Children's Hospital - **(801)662-2655**

Veteran Affairs Medical Center

If you are conducting inpatient or outpatient research at the VA, please contact the investigational pharmacist at the number listed below:
Veteran Affairs Medical Center - **(801)582-1565 ext. 1454**

The PI must agree to the Statement of Assurance when the PI uses the "Submit" activity to submit the application for IRB review. In the "Submit" activity window, a checkbox to accept this Statement of Assurance will be available. By checking the box, the PI agrees to the following:

- I have read and I understand the above information provided.

- I have reviewed the appropriate policies and procedures and/or have contacted the appropriate investigational pharmacist for my research involving an investigational agent.
- I understand the requirements regarding the distribution, storage, and control of investigational agent(s) for research purposes.

IRB_00116610 **Created:** 10/1/2018 12:13 PM

PI: Paul Bernstein M.D. **Submitted:** 11/21/2018

Title: Lutein & Zeaxanthin in Pregnancy (L-ZIP) - Carotenoid Supplementation During Pregnancy: Ocular and Systemic Effects

Investigational Drug Data Form

	Drug Name	Drug Accountability	Drug Supply Location
View	Lutein-2mg Zeaxanthin Softgels	The Kemin softgels will be stored in and dispensed by the Moran Eye Center Pharmacy. The prenatal multivitamin tables will be stored in the Moran Eye Center Clinical Studies Storage room and dispensed by the study coordinator. The softgels and multivitamins will only be accessible to authorized and trained staff members.	Moran Eye Center Pharmacy and Moran Eye Center Clinical Studies Storage Room

Investigational Drug Data Form

1. **Name of Investigational Drug:** Lutein-2mg Zeaxanthin Softgels
2. **Synonyms:**
   Softgel containing 10 mg lutein, 2 mg zeaxanthin, and safflower oil.
3. **Manufacturer or Other Source:** Kemin Health, Des Moines, IA
4. **Other Study Drugs:**
   Placebo softgel (Kemin Health) containing safflower oil (control group will receive).
   Prenatal vitamins (all participants will receive)
5. **Type of Study (Blinding Information):**
   Double-masked
6. **Strength(s) and Dosage Form(s):**
   The active study supplement, Kemin Health Lutein-2mg Zeaxanthin softgel, is a commercially available, over the counter product containing 10 mg of lutein and 2 mg zeaxanthin per softgel.
7. **Indications for Use and Pharmacology:**
   Nutritional supplement
8. **Possible Side-Effects/Adverse Reactions:**
   Kemin Health softgels with Lutein/zeaxathin are within the standard of care expectant mothers would receive if they were not in the study. There are no expected physical risks associated with the supplements.
9. **Drug Administration Information**
   a. **Usual Therapeutic Dose:**
      1 softgel per day (10 mg lutein, 2 mg zeaxanthin)
   b. **Dosage Range:**
      1 softgel per day
   c. **Therapeutic Blood Levels:**
      unknown (not routinely tested in standard care)
   d. **Route of Administration:**
      Oral
   e. **Rate of Administration for IV Infusion or Push:**
      N/A
   f. **Reconstitution Directions (include stability info):**
      N/A
   g. **Precautions and Special Instructions for Administration:**
      During pregnancy and lactation take one softgel daily with food.
   h. **Toxicology and Antidote:**
      There are no known toxic effects of taking too much zeaxanthin. Very large doses of carotenoids such as lutein and zeaxanthin can cause carotenodermia - a yellow-orange skin discoloration. It can look like jaundice, but the abnormal skin color can be removed with an alcohol swab. In case of

overdose do not induce vomiting. Contact Poison Control, physician or pharmacist for advice.

10. **Describe the plan to control, store, and dispense the investigational drug. This plan should ensure that the drug is only used by qualified investigator(s) for the participants enrolled in this research project.**
The Kemin softgels will be stored in and dispensed by the Moran Eye Center Pharmacy.

The prenatal multivitamin tables will be stored in the Moran Eye Center Clinical Studies Storage room and dispensed by the study coordinator.

The softgels and multivitamins will only be accessible to authorized and trained staff members.

11. **Location of Drug Supply:**

Other

Moran Eye Center Pharmacy and Moran Eye Center Clinical Studies Storage Room

12. **Storage Requirements:**

Room Temperature

If Other, Please Explain:
Store with cap secured at room temperature. Avoid extreme temperatures.

13. **Emergency Drug Information (include name and phone number):**
Paul Bernstein, MD, PhD
801-581-4069

Investigational Use of a Device

1. What is the initial risk determination of the device study according to the investigator and/or sponsor?

The study is a non-significant risk (NSR) device study.

a. Provide IDE (or HDE) Number(s) for significant risk devices:

IDE #	Device Name	IDE Holder

There are no items to display

b. Attach verification of the IDE number for significant risk devices to the Documents and attachments page. Please check the method by which you choose to verify the IDE number:

There are no items to display

2. Describe the plan to control, store, and dispense the investigational device. This plan should ensure that the device is only used by qualified investigator(s) for the participants enrolled in this research project.

There are two investigational devices being used in this study. The first is the Heidelberg MOPD module software program used to analyze carotenoid levels in the macula, the second is the skin scanner. Dr. Bernstein personally oversees the use of the Heidelberg system. He does not allow use of the software program for routine medical care. Dr. Bernstein is a patent holder for the scanner and personally control access to the scanner and train study staff in it's use. He does not allow use of the skin scanner for routine medical care, nor would it be relevant to standard care.

Non-Significant Risk Device

Review the following definition of a non-significant risk (NSR) device:

1. The medical device is not a significant risk device, because all of the following are true:
    a. The medical device is NOT intended as an implant that presents a potential for serious risk to the health, safety, or welfare of a subject.
    b. The medical device is NOT purported or represented to be for a use in supporting or sustaining human life that presents a potential for serious risk to the health, safety, or welfare of a subject.
    c. The medical device is NOT for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health that presents a potential for serious risk to the health, safety, or welfare of a subject.
    d. The medical device is does NOT otherwise present a potential for serious risk to the health, safety, or welfare of a subject.
2. The medical device is not banned.

1. **Provide justification of why the investigational medical device used in this study meets the definition of a NSR device.**
In this study, we are using the Heidelberg MultiColor Spectralis instrument to measure and image macular pigment optical density (MPOD). This commercial device is FDA cleared for use in eye clinics throughout the United States to image the retina in various ways. Heidelberg has provided us with a beta version of a software package which analyzes autofluorescence images to measure MPOD. Since this software has not yet been submitted to the FDA for approval, we can use it only under an IRB approved protocol. This software analyzes collected images in a new way, but the actual collection of the images is done in the usual manner for the instrument, so there are no significant risks of harm to the subjects.

The resonance Raman skin scanner measures carotenoids in the skin by shining a blue light on the palm of the hand for about 30 seconds. It is a higher sensitivity research version of the commercially available BioPhotonic scanner made by NuSkin/Pharmanex. The laser power is less than many laser pointers and is completely safe for prolonged skin exposure, so it poses no significant risk to the subjects.

Genetic Research

1. **Describe the risks to participants in regard to genetic testing, including applicable risks to privacy and confidentiality, as well as psychological and social risks.**

   Risks of Carotenoid and Control Supplements – Both kinds of supplements are within the standard of care expectant mothers would receive if they were not in the study. They pose no additional risk to participants.

   Risks of Visual acuity and contrast sensitivity – These are routine vision tests and pose no risk to participants above standard medical care.

   Risks of Ophthalmic imaging – Light levels projected on the retina during the photographs and macular pigment measurements are well within established safety limits. Participants may notice a central dark spot in their vision similar to the afterimage generated by a camera flash. This will fade in about 5 minutes. Infants may experience discomfort during the macular pigment imaging and foveal imaging. Parents may feel emotional distress when observing the infant undergoing this safe examination.

   Risks of Carotenoid skin measurements – There are no expected risks from the light exposure from the skin measurement. It is important not to look directly at the laser for a long period of time.

   Risks of Blood draws – Whenever possible the blood samples for this study will be taken at the same time participants are having blood drawn for routine prenatal blood work. The blood sample from the infants umbilical cord will be taken at the same time blood is collected for his/her routine care.

   Risks of Eye exams – The dilation drops used for the exams are considered standard of care for dilated eye exams during pregnancy.

   Risks of Nutrition surveys and supplement logs – recording diet and supplement intake will take a few minutes of participants time, but poses no risk.

   Risks of genetic research and sample banking - There is a potential risk of loss of confidentiality, but procedures are in place to make this highly unlikely.

   Unforeseeable Risks - In addition to the risks listed above, participants may experience a previously unknown risk of side effect.

2. **Describe the privacy protections in place for participants in regard to genetic testing. This includes how family member privacy will be protected.**
   In order to maintain subject privacy, study personnel will not discuss genetic testing with the participant unless they are in a private area.

3. **Are you performing whole genome or whole exome sequencing?**
   ○ Yes ● **No**

4. **Describe the confidentiality protections in place for participants' genetic information. Discuss if and how data will be shared and protected outside the local study team.**
   Genetic testing results will not be shared with participants or included in their medical record.

5. **Will incidental findings relevant to individuals or families be communicated to the participants?**
   ○ Yes ● **No**
   If yes, answer the questions below:

   a. **Describe the process for determining which incidental findings will be returned to the participants. Describe the information and expert consultation that will be used to make this determination.**

   b. **Indicate the process that will be used to return information about incidental finding to participants:**
   There are no items to display
   If Other, describe and justify the process that will be used:

6. **Will genetic information or samples be submitted to a national or international database because of this research?**

   ○ Yes

○ No

Data & Tissue Banking

1. **Select the items that will be banked:**
   - [x] **Biological samples**
   - [ ] Data

   Type(s) of samples to be collected:
   Blood, saliva and placenta tissue

2. **What type(s) of future research will be allowed on the data/samples?** Saliva and blood samples will be used for research related to the genetics of carotenoid metabolism.

   Placenta samples will be used to study maternal-infant carotenoid transport on a tissue level.

3. **Who manages the repository and where will the data/samples be stored?**
   Dr. Bernstein at the Moran Eye Center.

4. **Indicate whether the data/samples in the repository will be identifiable directly or through a code/link.**

   a. **Select one of the following options:**
   OPTION 1: All data/samples will be identifiable to one or more individuals who have responsibilities to manage or oversee the repository.

   b. **If you selected OPTION 1 or 2 above, describe the process for managing the identifiable data:**

   ### Who will manage and have access to the identifiable data?
   Dr. Bernstein and the Utah study team.

   ### Where will the data be kept?
   On paper study records, in the RedCap database created for this study and on University maintained computer servers.

   ### How will the data be kept confidential?
   The study team will protect study data according to HIPAA regulations and prohibit access to anyone who does not need the information in order to perform their job.

5. **Describe the procedures for participants to withdraw their data/samples from the repository. If participants will not be able to withdraw their samples, please provide an explanation:**
   Participants will need to contact Dr. Bernstein or a member of the study team and request their sample be withdrawn.

6. **Will future research results or findings be communicated to the participants?**
   ○ Yes ● **No**

7. **Describe the procedures for other researchers to obtain data/samples from the repository for use in future research.**
   Other researchers will need to provide proof of IRB approval for their project and an executed material transfer agreement, if applicable.

8. Resources and Responsibilities

1. * **State and justify the qualifications of the study staff:**

   Study physicians have a medical license allowing them to make medical decisions and provide patient care. They are qualified by certification and experience to conduct the study.

   Study Coordinators have experience in conducting clinical studies and receive protocol specific training from the sponsor, investigator and other study team members.

2. * **Describe the training that study staff and investigators will receive in order to be informed about the protocol and understand their research-related duties and functions:**

   Study specific training includes face to face training such as Investigator meetings or staff meetings, e-mail correspondence, webinars/teleconferences. All study staff members and investigators agree to conduct the study according to good clinical practices and the ethical conduct of research. Training documentation, including but not limited to study meetings, GCP certificates and CITI certificates will be maintained in the study file.

3. * **Describe the facilities where the research activities will be performed (e.g. hospitals, clinics, laboratories, classrooms/schools, offices, tissue banks, etc.).**

   Study visits will take place at the University of Utah hospital, Well Baby Nursery, OB/GYN outpatient clinic and Moran Eye center clinic.

   Study procedures and data collection will be conducted by staff from the OB/GYN department and the Moran Eye Center at the University of Utah.

   The study outcome data will be analyzed by a consultant from the University of Utah Study Design and Biostatistics Center of the Center for Clinical and Translational Science.

   Image analysis of retinal camera macular pigment measures will be conducted in Dr. Bernstein's laboratory.

   De-identified data (nutrition surveys) will be sent to Tufts University under an MTA. The MTA will be signed an kept with the research records.

   De-identified placenta samples will be sent to NYU Langone for analysis under an MTA.

4. * **Describe the medical or psychological resources available at this site (and other participating sites, if applicable) that participants might require as a consequence of the research. If not applicable, please state.**

   Medical resources at the Moran Eye Center and University of Utah Hospital and Clinics are available to treat any complications of the participants' eye conditions related to their participation in the research. The PI and the sub-investigators are always available to answer any questions that the participants may have and have the expertise to handle any medical issues that may arise.

IRB_00116610 **Created:** 10/1/2018 12:13 PM

PI: Paul Bernstein M.D. **Submitted:** 11/21/2018

Title: Lutein & Zeaxanthin in Pregnancy (L-ZIP) - Carotenoid Supplementation During Pregnancy: Ocular and Systemic Effects

Documents and Attachments

If any of your documents (such as investigational brochures, sponsor protocols, advertisements, etc.) are not available in an electronic format, please scan and save them as PDF files or contact our office for assistance.

Naming Documents: Please use the title field to clearly indicate the content of each form. The name you enter will be listed on your approval letter. Use names that will differentiate from earlier versions.

Examples:
Consent Document Control Group 04/14/05
Consent Document Treatment Group 4/14/05
Sponsor Protocol 04/14/05 Version 2
Assent Document(Highlighted Changes)

Apple/Macintosh Users:MS Word documents must have a .doc file extension. See ERICA home page for instructions.

Print View: IRB Draft Protocol Summary

eProtocol Summary:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Consent Documents, Consent Cover Letters, Consent Information Sheets, Consent Scripts, etc.:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Parental Permission Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Assent Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

VA Consent Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Surveys, Questionnaires, Interview Scripts, etc.:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Full Protocol (company protocol, sponsor protocol, investigator-initiated protocol, etc.):

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Investigational Brochure (IB) for Investigational Drug or Drug/Device Package Insert:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Grant Application:

The Federal Government is a direct or indirect sponsor of your research. You are required to provide a copy of the grant proposal, grant award, or sub-award.

By submitting to the IRB, you are confirming the grant and the study protocol are consistent (Design, Study Population, Study Objectives and Goals, Test Interventions and Procedures, etc.)

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Literature Cited/References:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Principal Investigator's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified	Date Approved
Bernstein CV 13 May 2015.pdf(0.01)	0.01	5/14/2015 1:10 PM	5/14/2015 1:10 PM	
Bernstein CV 13 Sep 2017.pdf(0.01)	0.01	1/9/2018 3:49 PM	1/9/2018 3:49 PM	
Bernstein CV exp 9.13.2021.pdf(0.01)	0.01	4/19/2021 12:42 PM	4/19/2021 12:42 PM	

Faculty Sponsor's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Other Stamped Documents:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Recruitment Materials, Advertisements, etc.:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Other Documents:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

PI: Paul Bernstein M.D. Submitted: 11/21/2018

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Finish Instructions

Finish Instructions

1. **To view errors, select the "Validate" option at the top-left of the page. If you have errors on your application, you won't be able to submit it to the IRB.**
2. **Selecting the Finish button will NOT submit the application to the IRB.**
   You MUST select the "Submit" option on the workspace once you've selected the "Finish" button.
3. **If your study has a faculty sponsor: Once the PI submits the application, it will be sent to the faculty sponsor for final approval. The IRB cannot review the study until the faculty sponsor submits the application to the IRB.**