

AGE-RELATED EYE DISEASE STUDY 2 PROTOCOL

Age-Related Eye Disease Study 2 (AREDS2): A Multi-center, Randomized Trial of Lutein, Zeaxanthin, and Omega-3 Long-Chain Polyunsaturated Fatty Acids (Docosahexaenoic Acid [DHA] and Eicosapentaenoic Acid [EPA]) in Age-Related Macular Degeneration

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This study is being conducted in compliance with the protocol, FDA regulations (21 CFR Parts 50, 54, and 56, 312), Good Clinical Practices, applicable local regulations, and the Declaration of Helsinki.

INVESTIGATOR STATEMENT OF APPROVAL

Age-Related Eye Disease Study 2 (AREDS2): A Multi-center, Randomized Trial of Lutein, Zeaxanthin, and Omega-3 Long-Chain Polyunsaturated Fatty Acids (Docosahexaenoic Acid [DHA] and Eicosapentaenoic Acid [EPA]) in Age-Related Macular Degeneration

I have read the Protocol and agree to follow the procedures as outlined in this Protocol.

I will not start the study until I have obtained written approval by the governing Institutional Review Board/Ethics Committee. I will obtain written informed consent from all study participants prior to conducting any study procedures.

I understand that my electronic or handwritten signature, or that of a co-investigator, on a case report form indicates that the data contained on that form have been reviewed and accepted as accurate by the signatory.

I agree to conduct this study in compliance with the applicable local regulations, FDA regulations (21 CFR 50, 54, 56, 312), Good Clinical Practices, and the Declaration of Helsinki.

I understand and am aware of my responsibilities as an Investigator as described in the applicable Good Clinical Practices regulations.

I understand that this protocol and related information is subject to the confidentiality terms found in my signed Confidentiality or Clinical Services Agreement. I agree to protect the confidentiality of my patients when allowing the Sponsor of this clinical trial and/or relevant regulatory authorities access to my medical records for AREDS2 participants.

Principal Investigator, Printed Name

Address:

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Principal Investigator, Signature

Date

Upon signing, send this page (original) to The EMMES Corporation for their files and keep a copy for your Regulatory Binder.

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Précis

Eye disorders presenting in late adulthood contribute a substantial burden to society as the primary cause of blinding conditions and low vision. The Eye Disease Prevalence Research Group estimates there are approximately 937,000 blind people residing in the United States; of these, approximately 841,000 (90%) are aged 60 years or older. Age-related eye disease will continue to be an issue of public health significance, since demographic shifts are projected to result in a 50% increase in the number of U.S. residents aged 65 years and older by the year 2020. The Age-Related Eye Disease Study 2 (AREDS2) is a National Eye Institute (NEI)-sponsored study of nutrient-based factors that may influence the development and progression of the two most prevalent age-related eye diseases: age-related macular degeneration (AMD) and cataract.

Human and animal studies provide a reasonable basis for speculating that certain nutrients accreted to and concentrated in the eye have the capacity to modulate factors and processes implicated in the pathogenesis of AMD and cataract. Results from the Age-Related Eye Disease Study (AREDS) on the relationship of lutein/zeaxanthin and omega-3 long-chain polyunsaturated fatty acid (LCPUFA) intake with advanced AMD are informative, yet the non-experimental sampling (observational) design limits our strength of inference.

AREDS2 is a multi-center Phase III randomized clinical trial designed to assess the effects of oral supplementation of high doses of macular xanthophylls (lutein and zeaxanthin) and/or omega-3 LCPUFAs as a treatment for AMD, cataract and moderate vision loss. In addition to this objective, the study will provide information on the clinical course, prognosis, and risk factors for development and progression of both AMD and cataract. Other study goals include the evaluation of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on the progression and development of AMD. AREDS2 will also seek to validate the fundus photographic AMD scale developed from AREDS.

1.0 Background and Rationale

AMD is a collection of clinically recognizable ocular findings that can lead to blindness. The findings include drusen, retinal pigment epithelial (RPE) disturbance (including pigment clumping and/or dropout), RPE detachment, geographic atrophy, subretinal neovascularization, and disciform scar. Not all these manifestations are needed for AMD to be considered present. The prevalence of ophthalmoscopically or photographically identifiable drusen increases with age, and most definitions of AMD include drusen as a requisite. However, drusen alone do not seem to be associated with vision loss. It is rather, the association of drusen with the vision-threatening lesions of AMD (geographic atrophy, RPE detachment, and subretinal neovascularization) that has led to their inclusion in the definition of AMD.

Existing treatments are of limited scope and efficacy; they are costly and may result in blinding complications. The Macular Photocoagulation Study (MPS), a multi-center, controlled, randomized clinical trial sponsored by NEI, has demonstrated the beneficial effects of laser photocoagulation in reducing the risk of vision loss from well-defined choroidal neovascularization in the exudative form of AMD.¹ Laser photocoagulation is not a cure for the neovascular form of AMD because many cases are not suitable for treatment and the beneficial effect of treatment appears to decrease over time. Photodynamic therapy (PDT) with verteporfin is a proven treatment for neovascular AMD.² PDT is a two-part process involving systemic administration of a photosensitizing drug, verteporfin, followed by non-thermal light application that activates the drug that is present in the macular neovascular complex. This treatment decreases the risk of vision loss but does not improve vision.

Pegaptanib (Macugen) is another FDA-approved therapy for the treatment of neovascular AMD. This treatment addresses the abnormal blood vessel growth and blood vessel leakage that is believed to be the underlying cause of the vision loss. Significant scientific evidence suggests that the presence in the eye of elevated levels of a protein known as vascular endothelial growth factor, or VEGF, plays an important

role in causing this abnormal blood vessel growth and blood vessel leakage. Macugen is an anti- VEGF therapy found to be beneficial in the treatment of neovascular AMD.³ In June 2006, Ranibizumab (LucentisTM) received FDA approval for the treatment of patients with neovascular age-related macular degeneration. Ranibizumab, an inhibitor of all forms of VEGF, is the first FDA-approved treatment for macular degeneration that significantly improves vision in a quarter to a third of patients and maintains or improves vision in greater than 90% of patients.⁴

While the neovascular form of the disease accounts for only 10 percent of all cases of AMD, 79 percent to 90 percent of all cases of legal blindness due to AMD are attributed to the neovascular form.⁵⁻⁶ Substantial central vision loss, including legal blindness, can also occur in the atrophic form of AMD, for which no treatment is currently available.

2.0 Scientific Rationale

The Retinal Disease Panel (RDP) of the *National Plan for Eye and Vision Research* has identified characterization of environmental effects on AMD etiology and the development of new AMD treatments as two of the four key programmatic goals of AMD research. Existing surgical and pharmacologic treatments for AMD are limited in scope and efficacy.

The RDP states that the leading cause of visual loss among elderly persons is AMD, which has an increasingly important social and economic impact in the United States. As the size of the elderly population increases in this country, AMD will become a more prevalent cause of blindness than both diabetic retinopathy and glaucoma combined. Although laser treatment has been shown to reduce the risk of extensive macular scarring from the “wet” or neovascular form of the disease, there are currently no effective treatments for the vast majority of patients with AMD.

The Eye Diseases Prevalence Research Group (EDPRG) attributes AMD as the major cause of blindness among elderly people of European ancestry. Among white persons, AMD is believed to account for more than 50% of all blinding conditions. The EDPRG

estimates that approximately 1.2 million residents of the US are living with neovascular AMD and 970,000 are living with geographic atrophy, while 3.6 million are living with bilateral large drusen. In the next 20 years these values are expected to increase by 50% with projected demographic shifts.⁷

Age-related developmental changes in retinal morphology and energy metabolism, as well as cumulative effects of environmental exposures may render the neural and vascular retina and retinal pigment epithelium more susceptible to damage in late adulthood. Along with these metabolic and structural changes and exposures, the aging eye also experiences a reduction in the potency of endogenous and exogenous defense systems. Pharmacological and surgical treatment options are of limited scope and efficacy currently. They are costly and may result in complications as severe as end-stage disease. The likelihood of vision loss among persons with neovascular AMD can be reduced with anti-VEGF treatment, photodynamic therapy, and laser photocoagulation.

Nutrient-based preventive treatments for AMD development and progression have been examined in AREDS, a NEI-sponsored study. AREDS was a multi-center study of the natural history of AMD and cataract. AREDS included a controlled randomized clinical trial designed to evaluate the effect of pharmacological doses of zinc and/or a formulation containing nutrients with antioxidant properties (vitamin C, vitamin E, and β -carotene) on the rate of progression to advanced AMD and on visual acuity outcomes.⁸ The use of the combination of antioxidants and zinc reduced the risk of development of advanced AMD in participants who had at least a moderate risk of developing AMD by about 25%. The overall risk of moderate vision loss [≥ 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart] was reduced by 19% at 5 years.

Of approximately 600 carotenoids identified in nature⁹, 50 in the human diet⁹, and 20 in human serum¹⁰, only two forms of dietary xanthophylls, lutein and zeaxanthin [(3R,3'R,6'R)- β , β -caroten-3,3'-diol)], are present in human macular pigment.¹¹ Lutein represents approximately 36% of all retinal carotenoids; zeaxanthin and meso-

zeaxanthin each represent about 18%. The natural tissue distribution, biochemical, and biophysical characteristics of lutein provide a reasonable basis for speculating that this nutrient acts in biological systems as: (1) an important structural molecule within cell membranes; (2) a short-wavelength light filter; (3) a modulator of intra- and extracellular reduction-oxidation (redox) balance; and (4) a modulator in signal transduction pathways.¹² Lutein and zeaxanthin were considered for inclusion in the AREDS formulation; however, at the time of AREDS' initiation, neither carotenoid was readily available for manufacturing in a research formulation.

LCPUFAs affect factors and processes implicated in the pathogenesis of vascular and neural retinal disease.¹³ Evidence characterizing structural and functional properties of LCPUFAs indicates that these nutrients may operate both as: (1) essential factors in the visual-sensory process, and (2) protective agents against retinal disease.

Docosahexaenoic Acid (DHA) is the major structural lipid of retinal photoreceptor outer segment membranes.¹⁴⁻¹⁵ Tissue DHA status affects retinal cell signaling mechanisms involved in phototransduction.¹⁶⁻¹⁷ Tissue DHA insufficiency is associated with conditions characterized by alterations in retinal function,¹⁸⁻²⁰ and functional deficits have been ameliorated with DHA supplementation in some cases.²¹ Biophysical and biochemical properties of DHA may affect photoreceptor function by altering membrane permeability, fluidity, thickness, and lipid phase properties.²²⁻²³ DHA may operate in signaling cascades to enhance activation of membrane-bound retinal proteins.^{16-17,24} DHA may also be involved in rhodopsin regeneration.²⁵

DHA and Eicosapentaenoic Acid (EPA) may serve as protective agents because of their effect on gene expression,²⁶⁻²⁹ retinal cell differentiation,³⁰⁻³² and survival.³⁰⁻³⁴ DHA activates a number of nuclear hormone receptors that operate as transcription factors for molecules that modulate redox-sensitive and proinflammatory genes; these include the peroxisome proliferator-activated receptor- α (PPAR- α)²⁷ and the retinoid X receptor (RXR).²⁶ In the case of PPAR- α , this action is thought to prevent endothelial cell dysfunction and vascular remodeling through inhibition of vascular smooth muscle cell

proliferation, inducible nitric oxide synthase production, interleukin(IL)-1 induced cyclooxygenase (COX)-2 production, and thrombin-induced endothelin-1 production.³⁵

Research on model systems demonstrates that omega-3 LCPUFAs also have the capacity to affect production and activation of angiogenic growth factors,³⁶⁻³⁸ arachidonic acid-based proangiogenic eicosanoids,³⁹⁻⁴³ and matrix metalloproteinases involved in vascular remodeling.⁴⁴ EPA depresses vascular endothelial growth factor (VEGF) –specific tyrosine kinase receptor activation and expression.^{36,45} VEGF plays an essential role in induction of endothelial cell migration and proliferation, microvascular permeability, endothelial cell release of metalloproteinases and interstitial collagenases, and endothelial cell tube formation.⁴⁶ The mechanism of VEGF receptor down-regulation is believed to occur at the tyrosine kinase nuclear factor-kappa B (NFkB) site because EPA treatment causes suppression of NFkB activation. NFkB is a nuclear transcription factor that up-regulates COX-2 expression, intracellular adhesion molecule (ICAM), thrombin, and nitric oxide synthase. All four factors are associated with vascular instability.³⁵ COX-2 drives conversion of arachidonic acid to a number of angiogenic and proinflammatory eicosanoids.

The evidence base suggests that macular xanthophylls and omega-3 LCPUFAs may act as modifiable factors capable of modulating processes implicated in AMD pathogenesis and progression. Intake of these compounds may also show merit as a well-tolerated preventive intervention. Biochemical and biophysical properties of these compounds demonstrate a capacity to modulate factors and processes that activate and are activated by exposures associated with aging. These exposures include developmental changes associated with aging, chronic light exposure, alterations in energy metabolism, and cellular signaling pathways.

An inverse relationship of dietary omega-3 LCPUFA intake with advanced AMD has been reported in all six studies examining the issue.⁴⁷⁻⁵² For prevalent disease, the magnitude of odds ratios for highest v. lowest omega-3 LCPUFA intake ranged from 0.4 to 0.9. Among these studies, the one containing the largest number of subjects with

neovascular AMD yielded a significantly lower likelihood of having the disease among participants reporting the highest consumption of omega-3 LCPUFAs. Five of six studies examining the association of dietary lutein/zeaxanthin intake with advanced AMD have yielded inverse relationships that are statistically significant.⁵³⁻⁵⁸ The magnitude of odds ratios in these studies ranged from 0.1 to 0.7. Both sets of findings are germane in guiding applied clinical research on prevention and treatment of retinal disease, since: (1) tissue concentrations of DHA, lutein, and zeaxanthin per unit area are substantially higher in the retina than elsewhere in the body; and (2) retinal tissue status of these compounds is modifiable and dependent upon intake.

There is a compelling need to implement a clinical trial on nutrients that are both concentrated in the retina and implicated in modulation of pathogenic factors and processes of AMD.

3.0 Study Objectives

The primary objective of AREDS2 is to evaluate the effect of dietary xanthophylls (lutein/zeaxanthin) and/or omega-3 LCPUFAs (DHA and EPA) on progression to advanced AMD. This objective will be accomplished by collecting and assessing the data on approximately 4,000 AREDS2 participants aged 50 to 85 years, who at the time of enrollment, have sufficiently clear lenses for quality fundus photographs and have either: 1) bilateral large drusen or 2) large drusen in one eye and advanced AMD (neovascular AMD or central geographic atrophy) in the fellow eye.

The objectives of AREDS2 are to:

1. Study the effects of high supplemental doses of the dietary xanthophylls (lutein and zeaxanthin) and omega-3 LCPUFAs (DHA and EPA) on the development of advanced AMD.
2. Study the effects of these supplements on moderate vision loss (doubling of the visual angle or the loss of 15 or more letters on the ETDRS chart).
3. Study the effects of these supplements on cataract.

4. Study the effects of eliminating beta-carotene in the original AREDS formulation on the development and progression of AMD.
5. Study the effects of reducing zinc in the original AREDS formulation on the development and progression of AMD.
6. Validate the fundus photographic AMD scale developed from the Age-Related Eye Disease Study.

4.0 Study Design and Methods

AREDS2 is a multi-center randomized trial of 4,000 participants designed to assess the effects of oral supplementation of high doses of macular xanthophylls (lutein and zeaxanthin) and/or omega-3 LCPUFAs (DHA and EPA) for the treatment of AMD and cataract. All participants will be offered additional treatment with the study formulation used in AREDS, but some participants will refuse to take the AREDS formulation for various reasons. For those who elect to take this additional supplement, which is now considered the standard of care, further randomization may occur to evaluate the possibility of deleting beta-carotene and decreasing the original levels of zinc in the formulation for the treatment of AMD, if consent is obtained. There will likely be a small proportion of the participants who would prefer not to be randomly assigned to these formulations but who will continue to take the original AREDS formulation. The development of advanced AMD will be documented by fundus photography, and the lens opacity outcome will be documented by red reflex photographs [cortical and posterior subcapsular (PSC) opacities] and history of cataract surgery. Before randomization, participants will have a run-in period of one month during which they will receive a month's supply of the following daily dose: one placebo lutein/zeaxanthin tablet, two placebo DHA/EPA capsules and two soft gel capsules of the AREDS formulation. For participants who currently smoke or quit smoking within the last year, a month's supply of placebo lutein/zeaxanthin tablets and placebo DHA/EPA capsules will be the only run-in medications administered.

Study participants will be assigned randomly to take one of the following Study Supplements on a daily basis: 1) Placebo, 2) Lutein/zeaxanthin, 3) DHA/EPA, or 4) Lutein/zeaxanthin and DHA/EPA.

Primary Randomization Agents

Placebo	Lutein/zeaxanthin	DHA/EPA	Lutein/Zeaxanthin + DHA/EPA	
	10 mg/2 mg	350 mg/650 mg	10 mg/2 mg	350 mg/ 650 mg

Participants will be offered the AREDS formulation. Those who agree to take the AREDS formulation and consent to a second randomization will be randomized to receive one of four alternative AREDS formulations in addition to the study supplements described above:

Secondary Randomization Agents (AREDS-Type Supplement)

Formulations	Vitamin C	Vitamin E	Beta Carotene	Zinc Oxide	Cupric Oxide
1	500 mg	400 IU	15 mg	80 mg	2 mg
2	500 mg	400 IU	0 mg	80 mg	2 mg
3	500 mg	400 IU	0 mg	25 mg	2 mg
4	500 mg	400 IU	15 mg	25 mg	2 mg

Note: There will be no placebo in this second-tier randomization, as treatment is considered standard of care.

If the participant is a current smoker or a former smoker that has quit within the last year, he or she will be randomized to one of the two arms without beta-carotene (Formulations 2 or 3). If a participant does not consent to randomization but wants to take the AREDS formulation, he or she will be provided the supplements provided that they are not a current smoker or a former smoker that has quit within the last year.

All participants taking a daily multivitamin and/or multimineral supplement will be asked to replace it with Centrum Silver[®]. This product will be provided free-of-charge.

4.1 Outcomes

The primary outcome of this study will be progression to advanced AMD based on AREDS2 Reading Center grading of fundus photographs in a study eye, as defined in Section 4.2. A study eye is defined as an eye without advanced AMD, confounding ocular lesion and without laser or other targeted treatment for drusen. Secondary and tertiary outcomes include:

- Comparison of the three active treatment arms to placebo on the progression to moderate vision loss;
- Effect of lutein/zeaxanthin and DHA/EPA on the progression of lens opacity or incidence of cataract surgery;
- Comparison of the three active treatment arms to placebo on vision loss (such as a 10-letter loss) and moderate improvement in participants with advanced AMD;
- Effect of eliminating beta-carotene in the original AREDS formulation on the progression and development of AMD;
- Effect of reducing zinc in the original AREDS formulation on the progression and development of AMD;
- Effect of eliminating beta-carotene in the original AREDS formulation on moderate vision loss;
- Effect of reducing zinc in the original AREDS formulation on moderate vision loss;
- Validation of the fundus photographic AMD scale developed from the Age-Related Eye Disease Study;
- Effect of lutein/zeaxanthin and/or DHA/EPA on movement on the AREDS AMD simple scale;
- Effect of eliminating beta-carotene and/or reducing zinc on movement on the AREDS AMD simple clinical scale;
- Effect of lutein/zeaxanthin and/or DHA/EPA on cognitive function as measured by the various instruments included in the AREDS2 Cognitive Function Telephone Battery; and
- Effect of DHA/EPA on cardiovascular morbidity and/or mortality.

Additional outcomes may be added during the course of the study.

4.2 Definitions

Advanced AMD: Atrophic or neovascular changes of AMD based on the examination of fundus photographs that include one or more of the following:

- (a) Definite geographic atrophy definitely or questionably involving the center of the macula (minimum diameter for a patch of atrophy to be classified as geographic is 360 μ M)
- (b) Evidence suggesting choroidal neovascularization.
At least two of the following:
 - (1) Serous detachment of the sensory retina
 - (2) Subretinal hemorrhage
 - (3) Retinal pigment epithelial detachment (PED) excluding drusenoid type
 - (4) Fibrous tissue
 - (5) Hard exudate
- (c) Definite disciform scar
- (d) Treatment for AMD (e.g., photodynamic therapy, anti-angiogenic therapy, etc) with accompanied evidence suggesting choroidal neovascularization documented by fundus photographs, fluorescein angiograms (FA) or optical coherence tomography (OCT).

Advanced AMD events may be reviewed by the AREDS2 Reading Center in the context of fluorescein angiograms and/or OCT readings taken at the time of the clinical diagnosis of progression to advanced AMD.

4.3 Inclusion Criteria

Children are not included because AMD is, by definition, an adult disease.

1. Men and women aged 50 to 85 years at the Qualification Visit.
2. Bilateral large drusen (\geq 125 microns) or large drusen in one eye and advanced AMD in the fellow eye. A study eye (eye without advanced

AMD) may have definite geographic atrophy not involving the center of the macula without evidence of drusen.

3. Study eye(s) with fundus photographs assessed by the Reading Center to be of adequate photo quality.
4. Pupillary dilation ≥ 5 mm in each eye for all participants, except that dilation < 5 mm in an aphakic or pseudophakic eye will not exclude a participant with adequate quality fundus photographs.
5. Randomization within three months following the Qualification Visit.
6. Willingness to stop taking any supplements containing lutein, zeaxanthin, omega-3 LCPUFAs (specifically DHA and EPA), vitamin C, vitamin E, beta-carotene, zinc or copper, other than those supplied by AREDS2. Willingness to stop taking other supplements is demonstrated by refraining from use of vitamin or mineral supplements that are part of the randomized trial during the entire run-in period. Continued use of nutritional supplements that are not part of the randomized trial (e.g., calcium) does not exclude a participant, provided that these supplements are taken one to two hours before or after the study supplements. If the participant wants to continue taking a multivitamin and/or multimineral supplement during the study he/she will be provided Centrum Silver®.
7. Demonstration that at least 75 percent of run-in medication was consumed, as determined by an estimated count of the remaining run-in tablets/capsules (exceptions may be made by appeal to the AREDS2 Coordinating Center) and willingness to take the randomized trial supplements for the next five years.
8. Likelihood, willingness, and ability to undergo examinations at yearly intervals for at least five years.
9. People who currently smoke are eligible to enroll in this study. However if the smoker elects to participate in the AREDS-type supplement (ATS) formulation randomization, they will be randomized to one of the two arms of the AREDS formulation without beta-carotene.

10. Ability and willingness to consent to both the Qualification and the Randomization/Follow up phases of the study. Participants will be provided a Participant Information Booklet (Appendix A) that will explain the overall study. For clinical sites using two consent forms, the First Informed Consent describes the responsibilities of the participant and the study during the run-in period. The Second Informed Consent describes responsibilities following randomization. For clinical sites using the AREDS2 Central IRB or whose local IRB requests it, the information in the First and Second Informed Consent has been combined into one document that must be signed at the Qualification Visit. Model informed consent forms are provided in Appendix B. For sites using two consent forms, an AREDS2 Second Informed Consent must be signed even if a First Informed Consent was signed previously.
11. Participants with advanced AMD in one eye may have received treatment for advanced AMD in the eye identified as having advanced AMD. These treatments include: intravitreal injections of pharmacological agents (i.e. Avastin®, Lucentis™, Macugen®, Kenalog, and others), laser, photodynamic therapy and others. However, a participant is not eligible if the fellow (study) eye has ever received any of these treatments for advanced AMD.

4.4 Exclusion Criteria

1. Ocular disease in *either* eye, other than AMD, which may confound assessment of the retina, including:
 - a. Diabetic retinopathy unless retinopathy is limited to fewer than 10 microaneurysms and/or small retinal hemorrhages,
 - b. Angioid streaks,
 - c. Central serous choroidopathy,
 - d. Surface wrinkling retinopathy (epiretinal membrane) that is more severe than the mild surface wrinkling retinopathy,
 - e. Optic atrophy,

- f. Pigmentary abnormalities considered by the Clinical Center ophthalmologist to be less typical of AMD than of some other condition, such as pattern dystrophy or chronic central serous retinopathy,
 - g. Myopic crescent of the optic disc the width of which is $\geq 50\%$ of the longest diameter of the disc, or pigmentary abnormalities in the posterior pole considered by the clinic ophthalmologist more likely to be due to myopia than to AMD,
 - h. Macular hole or pseudohole,
 - i. Retinal vein occlusion, active uveitis, presumed ocular histoplasmosis syndrome, other sight-threatening retinopathies, and other retinal degenerations, significant explained or unexplained visual field loss, or any other type of retinopathy or retinal degeneration,
 - j. A choroidal nevus within 2 DD of the center of the macula associated with depigmentation or overlying atypical drusen.
 - k. Epiretinal membrane of significant size located in the macular area that potentially can cause vision loss.
 - l. Other ocular diseases or conditions, the presence of which may now or in the future complicate evaluation of AMD.
 - m. Amblyopia (in study eye only)
2. Previous retinal or other ocular surgical procedures, the effects of which may now or in the future complicate assessment of the progression of AMD. Examples are argon laser trabeculoplasty, radial keratotomy, trabeculectomy, cryosurgery (except to repair a peripheral retinal hole), lamellar keratoplasty, pterygium surgery that affects or threatens the visual axis, radiation for ocular tumor, or repair of corneal or sclera laceration. Cataract surgery more than three months prior to randomization is not an exclusion criterion unless complicated by a condition that is causing or is likely to cause a decrease in visual acuity. Laser photocoagulation

for drusen and non-choroidal neovascularization in the non-study eye will not be exclusion factors.

3. Chronic requirement for any systemic or ocular medication administered for other diseases such as glaucoma and known to be toxic to the retina or optic nerve, such as:
 - a. Deferoxamine
 - b. Chloroquine/Hydroxychloroquine (Plaquinil)
 - c. Tamoxifen
 - d. Chlorpromazine
 - e. Phenothiazines
 - f. Chronic systemic steroid use of at least 10 mg per day or more
 - g. Ethambutol
4. Unwillingness or inability to stop taking supplements containing lutein, zeaxanthin, omega-3 LCPUFAs, vitamin C, vitamin E, beta-carotene, zinc or copper during the run-in period and for the next five years, or failure to take at least 75 percent of run-in medication as determined by an estimated count of placebo tablets and capsules (exceptions may be made by appeal to the AREDS2 Coordinating Center).
5. Participants supplementing with 2 mg or more of lutein and/or 500 mg or more of omega-3 long-chain polyunsaturated fatty acids (DHA and EPA) for a period of 1 year or more prior to the date of randomization. **A participant is eligible for the study if he/she agrees to refrain from taking these supplements during the Qualification period.**
6. Intraocular pressure 26 mm Hg or higher, or if there is some reason to believe that the participant may have glaucoma (e.g., history of the diagnosis of glaucoma, past or present use of medications to control intraocular pressure, or disc/nerve fiber layer defects suggestive of glaucoma), then the absence of a glaucomatous visual field defect must be documented by a normal Goldmann,

Humphrey, or Octopus perimetry test within 6 months prior to qualification. (In the judgment of the investigator, the participant may be ineligible due to glaucoma based upon IOP measurements, disc/nerve fiber layer defects suggestive of glaucoma, and visual field abnormalities).

7. Cataract surgery within three months or capsulotomy within six weeks prior to the Qualification Visit.
8. History of lung cancer.
9. Any systemic disease with a poor five-year survival prognosis (e.g. cancer, cardiovascular disease). If a vascular condition appears stable and the initial event occurred more than 12 months ago, the participant is eligible for the study.
10. Hemochromatosis, Wilson's Disease, or recent diagnosis of oxalate kidney stones.
11. Participant that has any condition that would make adherence or follow-up to the examination schedule of annual intervals for at least five years difficult or unlikely (e.g., personality disorder, use of major tranquilizers such as Haldol or Phenothiazine, chronic alcoholism or drug abuse).
12. Current participation in other studies that is likely to affect adherence with the AREDS2 follow-up schedule.
13. Participant is taking a systemic anti-angiogenic (such as squalamine lactate, avastin, etc.) for treatment of choroidal neovascularization or cancer. The use of intravitreal anti-VEGF such as Avastin®, Lucentis™, or Macugen®, in the eye that had advanced AMD at baseline is allowed. However, a participant is not eligible if the fellow (study) eye has ever received any of these treatments for advanced AMD.

4.5 Enrollment, Recruitment, and Follow-up Requirements

Participants are expected to be enrolled from up to 100 sites in the United States over a 15-month period. All enrolled participants will be followed until the last participant has completed five years of follow-up, or until the Data and Safety Monitoring Committee (DSMC) has recommended earlier trial termination.

4.6 Study Supplement Administration/Concomitant Medications

After the participant is determined eligible by the investigator, has completed the run-in period, and has signed the Second Informed Consent, the participant will be enrolled into the study. The EMMES Corporation (the AREDS2 Coordinating Center) will randomly assign participants to treatment assignments. The participant will then receive the treatment(s) assigned to that identification number.

Participants will be asked to take one tablet (lutein/zeaxanthin 10mg/2mg or lutein/zeaxanthin placebo) and two soft-gel capsules (DHA/EPA 350mg/650mg or DHA/EPA placebo) with breakfast each day. If the participant agrees to participate in the AREDS-type supplement (ATS) trial he or she will also be asked to take two ATS soft-gel capsules (one capsule taken in the morning with food and one capsule taken in the evening with food). If the participant does not agree to participate in the ATS trial but wishes to continue taking the standard ATS, and he or she is a non-smoker or quit smoking more than one year prior to qualification, two daily soft-gel capsules of the ATS will be provided. The participant will be instructed to consume one capsule in the morning with food and one capsule in the evening with food. Participants are required to bring their full or partially full bottles of study supplements to each in-clinic visit for pill counts to assess compliance. Participants currently supplementing with a multivitamin and/or multimineral formulation who wish to continue this practice will be provided Centrum Silver[®] and will be reminded not to take other “non-study” multivitamins or extra supplements containing the nutrients used in AREDS2. Participants may continue to take nutritional supplements that are not part of the randomized trial (e.g., calcium, herbal supplements), provided that these supplements are taken one to two hours

before or after the study supplements. Participants will receive an initial supply of AREDS2 supplements at the Randomization Visit.

4.7 Examination Requirements

4.7.1 Qualification Visit

The Qualification visit consists of the following examinations and procedures:

1. Explanation of AREDS2 and a copy of the Participant Information Booklet (if not mailed ahead of the visit)
2. Signing of the First Informed Consent that describes participant rights during the qualification period
3. Complete medical and ocular history
4. Manifest refraction (optional)
5. Visual acuity examination via the Electronic Visual Acuity Tester (EVA) using the Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol found on the AREDS2 Web site (optional)
6. Ocular examination
7. Fundus photographs (3-standard field stereoscopic and red reflex)*

*See the AREDS2 Fundus Photograph Reading Center Manual of Procedures for additional details.

Potential participants will be given:

1. Three bottles of run-in supplements and instructions for taking the supplements (smokers will receive two bottles of run-in supplements).
2. A postcard to notify the clinic when the run-in supplement is stopped.
3. A reminder to bring the run-in supplement bottles to the Randomization Visit.

The participant may be mailed the Participant Information Booklet.

4.7.2 Randomization Visit

Qualified participants will be asked to return to the clinic within 30 to 90 days after the Qualification Visit. Randomization will occur only after the participant is confirmed to be eligible. Participants are considered eligible if they return to the clinic within 90 days following the Qualification Visit, have good quality photographs as determined by the Reading Center, consume at least 75 percent of the run-in medication, and sign the randomization consent form.

Participants must be re-qualified if randomization does not occur within 90 days of the Qualification Visit. Re-qualification requires that the responses to each of the eligibility questions be verified and fundus photographs re-performed. The participant may return for the Randomization Visit as soon as the Reading Center assessment of the quality of the photographs has been made.

The AREDS2 Advantage Electronic Data Capture system (AdvantageEDCSM) will assign bottle numbers. The master randomization list for each center is maintained at the AREDS2 Coordinating Center. In the unlikely event of computer failure, randomization may be performed by calling the AREDS2 Coordinating Center Monday through Friday from 9:00 a.m. to 5:00 p.m. Eastern Time.

The Randomization Visit consists of the following examinations and procedures:

1. Signing of the Second Informed Consent that describes the randomization and responsibilities for continued participation in AREDS2 (if a combined consent not signed at the Qualification Visit)
2. Determination of adherence – participants who appear to have been unable or unwilling to take at least 75 percent of their run-in supplements will be ineligible
3. Manifest refraction

4. Visual acuity examination via the Electronic Visual Acuity Tester (EVA) using the Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol found on the AREDS2 Web site
5. Ocular Examination
6. Food Frequency Questionnaire (FFQ)
7. Family history questionnaire
8. Distribution of Study Supplements and Centrum Silver[®], if applicable
9. Nutritional biochemistry sample (in selected clinics)*
10. Assignment of Bottle Numbers
11. Signing of Medical Record Release form

*Please refer to the study Manual of Procedures for full details of the procedures.

Participants will be asked to participate in the AREDS2 cognitive function study. Participants who consent to participate will be contacted by telephone within three months after the Randomization Visit and asked to complete a 30- to 40-minute cognitive function battery. Please refer to the study Manual of Procedures for additional information regarding the cognitive function study.

4.7.3 Follow-up Visits

In-clinic follow-up visits will occur annually post-randomization. Telephone contacts will occur three- and six-months post-randomization and annually thereafter starting at 18 months post-randomization. These telephone contacts will be used to collect information about adverse events and compliance to study supplements. Collection of documents via contracted individuals at the University of Virginia, (e.g. discharge summaries, etc.) required as part of the Cardiovascular Outcome Study and/or death certificates, will occur subsequent to follow-up visits or telephone contacts, if applicable.

The in-clinic follow-up visits will consist of the following examinations and procedures:

1. Manifest refraction
2. Visual acuity examination via the Electronic Visual Acuity Tester (EVA) using the Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol found on the AREDS2 Web site
3. Ocular examination
4. Fundus photographs (3-standard field stereoscopic and red reflex)*
5. Adverse Event assessment
6. Collection and re-issuance of study supplement bottles
7. Assessment of supplement adherence
8. Nutritional biochemistry sample (in selected clinics) to be collected at the years 1, 3 and 5 follow-up visits.*
9. The Cognitive Function Telephone Battery will be administered to participants at the years 2, 4 and 6 (for those who have six years) follow-up visits.

The study flow chart can be found in Appendix C.

*Please refer to the study Manual of Procedures for full details of the procedures.

4.8 Study Assessments

4.8.1 Fundus Photography and Ocular Examination

Pupils will be dilated to 6 mm or larger with two sets each of 2.5% Neo-Syneprine and 1% Mydracyl, or equivalent. Contact lens examinations should be avoided prior to photography. A modified 3-standard fields color photography and fundus reflex procedure will be used in AREDS2. All photographs, from qualification through follow-up visits, will be read by a central reading center for an independent assessment. See the AREDS2 Fundus Photograph Reading Center Manual of Procedures for additional details.

4.8.2 Refraction and Best-Corrected Visual Acuity (BCVA)

Manifest refraction and BCVA measurement should be performed with the Electronic Visual Acuity Tester (EVA) using the Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol. This protocol has been developed to provide a visual acuity score that is comparable to the score achieved with the manual testing protocol used in the Early Treatment Diabetic Retinopathy Study (ETDRS). Refraction and BCVA testing by E-ETDRS protocol are detailed in the EVA and ETDRS Visual Acuity and Refraction Protocols located on the AREDS2 Web site. Specified personnel will receive training in these protocols and be certified as having received such training.

4.8.3 Fluorescein Angiography (FA)

FAs taken as standard of care will be requested if the participant is treated for CNV during the course of the study (specifically, the closest FA prior to the time of treatment will be requested). Standard fluorescein fundus photographic equipment may be used. Angiogram measurements will be performed to measure the extent of area of fluorescein leakage measured on FAs using a calibrated grid. All fluorescein images will be read by a central reading center for an independent assessment. See the AREDS2 Fundus Photograph Reading Center Manual of Procedures for additional details.

4.8.4 Optical Coherence Tomography (OCT)

OCTs taken as standard of care will be requested if the participant is treated for CNV during the course of the study (specifically, the closest OCT prior to the time of treatment will be requested). OCT will be utilized to assess subretinal fluid, intraretinal thickness, and choroidal neovascularization. All OCT images will be read by a central reading center for an independent assessment. See the AREDS2 Fundus Photograph Reading Center Manual of Procedures for additional details.

4.8.5 Food Frequency Questionnaire (FFQ)

A FFQ (Harvard Dietary Assessment) will be administered to participants at randomization. The FFQ will be used to assess habitual dietary intake. See the AREDS2 Manual of Procedures for additional details.

4.8.6 Nutritional Biochemistry

The Nutritional Biochemistry Study will be performed as a substudy at selected centers. Blood specimens will be collected for all consenting participants at the selected centers. The central laboratory will measure serum concentrations of vitamins A and E (alpha- and gamma-tocopherol), lutein, zeaxanthin, alpha- and beta-carotene, beta-cryptoxanthin, lycopene (trans-and total), selected fatty acids including DHA and EPA, zinc and copper. Blood specimens will be collected at randomization, year 1, year 3 and year 5. Biochemical testing will be performed by a central laboratory. Test results will be used to assure participant compliance and whether effective concentrations were achieved with the various AREDS2 interventions. See the AREDS2 Manual of Procedures for additional details.

4.8.7 Cardiovascular Outcome Study

The Cardiovascular Outcome Study will be performed as a substudy at all centers. After randomization, an AREDS2 participant may be hospitalized, experience a new or recurrent myocardial infarction or stroke, develop congestive heart failure (with subsequent hospitalization) or unstable angina, or undergo a cardiovascular procedure. These events will be part of the cardiovascular outcome study and will require physician adjudication.

Since adjudication requires obtaining information from medical records, each AREDS2 Clinical Site should have the participant sign a "Release of Medical Records". A template form is provided in Appendix D of the AREDS2 Protocol. At each visit, participants will be asked if they experienced any cardiovascular or cerebrovascular events since the last study visit. Participants will be asked to sign a medical release form for each event indicating their consent to release

medical records and have them reviewed by individuals other than themselves. All centers will then complete the appropriate case report forms (CRFs; Death, Hospitalization, or Outpatient Procedure and Cardiovascular Outcomes Report Form) and fax the Cardiovascular Outcomes Report Form and the signed medical release form to the University of Virginia (UVA). Adjudicators will then review both the medical records and CRFs to determine if the event meets one of the pre-defined cardiovascular outcomes. See the AREDS2 Manual of Procedures for additional details.

4.9 Randomization, Masking and Unmasking

The AREDS2 Coordinating Center will randomly assign the study supplements. Participants and investigators will be masked to the treatments. Participants will be unmasked if deemed clinically necessary by the examining physician and if the Study Chair and Data Safety and Monitoring Committee (DSMC) Chair are in agreement. A written request for unmasking, after approval by the Study Chair and DSMC Chair, will be made to the Coordinating Center, who will inform the site Principal Investigator of the treatment assignment. All instances of unmasking must be reported to the IRB, the DSMC and the FDA.

5.0 Monitoring Participants and Criteria for Withdrawal

5.1 Data Safety and Monitoring Committee

A Data and Safety Monitoring Committee (DSMC) is responsible for reviewing and approving the study design and, as appropriate, recommending design changes. In addition, the DSMC assesses study data with particular consideration of participant safety. The DSMC will convene prior to the initiation of the study to review the protocol. The Committee will review accumulated data on a regular basis, but may convene ad hoc meetings to address any significant problems. Problems related to participant safety may be brought to the DSMC's attention by any study participant or investigator. In reviewing the accumulated data, the Committee will consider whether protocol modifications are necessary or whether the study should continue without modifications.

If the Committee indicates changes in the protocol, recommendations will be made to the Operations Committee. The Operations Committee will consider and act on such recommendations in a timely manner.

5.2 Adverse Experience Reporting

All adverse events (as defined in Section 5.2.3), either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported. Any serious adverse event (SAE) regardless of severity or potential association with the study supplements, must be documented in study records by the site Investigator and promptly reported to the Coordinating Center (within 24 hours of learning about the event). Non-serious adverse events can be collected in a routine manner using case report forms.

5.2.1 Obligations of Site Investigators

AREDS2 requires the site Investigators to report all adverse events (as defined in Section 5.2.3), regardless of their severity or potential association with the study supplements. When submitting adverse event information to the Coordinating Center, a site Investigator may not delegate someone other than a listed study physician the responsibility for reviewing the accuracy of the contents of the adverse event report. When reporting an adverse event, the site Investigator must assign a severity grade to each event (see Section 5.2.5) and also declare an opinion on the relatedness of the event to the study supplements (see Section 5.2.6).

Serious adverse events are defined in section 5.2.3.1. For any such event, the Coordinating Center must be notified within 24 hours of when the Investigator first learns of the occurrence of the event. Adequate information must be collected with supporting documentation and entered into the AdvantageEDC data collection system. This data entry serves as notification of the Coordinating Center.

For adverse events considered non-serious, timely reporting is considered acceptable within seven days of learning about the event.

For all serious adverse events, the 24-hour reporting deadline is necessary to provide adequate time to investigate the report and determine if the serious adverse event requires further reporting. The Coordinating Center and/or NEI would then prepare materials to submit, if necessary, to regulatory authorities and IRBs within the timeframes required by regulation for expedited safety reports.

5.2.1.1 Serious Adverse Event Reporting Responsibilities of the Site

When an SAE is identified, the site Investigator (or the site Study Coordinator) shall promptly:

- A. Notify the site PI (if a different person) in person or by telephone about the SAE.
- B. Use the AdvantageEDCSM system to prepare the available serious adverse event information on a study adverse event case report form. If supplementary information is to be supplied, this may be attached to the SAE form in AdvantageEDCSM. If the data system is not available, use a MedWatch Form FDA 3500A or another designated reporting form and fax to the Coordinating Center. The event must be entered into AdvantageEDCSM as soon as the system is available.
- C. The site PI (or another designated study physician) is responsible for reviewing and approving the serious adverse event report contents (including the event description, grading of event severity, and attribution of relatedness to the study supplements).
- D. Submit the initial serious adverse event report to the AREDS2 Coordinating Center within 24 hours of recognizing the event. Submission to the local IRB is based on each site's responsibilities per the site's IRB.
- E. The adverse event report and each page of any attached materials must describe the study participant only by their coded study

identifier(s). Any personally identifying information (e.g., name, telephone number, address, etc.) must be removed or obscured before delivery to the Coordinating Center. Transmission may be done electronically via the AdvantageEDCSM system or by facsimile transmission to 877-804-9618. Any information that cannot be submitted via the AdvantageEDCSM system to the Coordinating Center must be sent by facsimile transmission.

- F. Contact the Protocol Monitor assigned to your site and verify receipt of the report by the Coordinating Center. If the Coordinating Center does not acknowledge receipt of the report within 48 hours of submission, make direct contact with the Protocol Monitor or her/his alternate contact to determine the report status.
- G. If the Coordinating Center requests additional information, or if further pertinent details become available (e.g., laboratory reports, follow-up evaluations, discharge summaries, autopsy reports, etc.), promptly submit them to the Coordinating Center through AdvantageEDCSM.
- H. If a death occurred, complete the death case report form. Be sure to include a statement regarding the causality assessment on the form.
- I. If a hospitalization occurred for more than 24 hrs, complete a serious adverse event form.

5.2.1.2 Submitting an Expedited Safety Report to the Local/Central IRB

When the Coordinating Center or the NEI informs a site that expedited safety reporting to regulatory authorities is required, the PI should review and update any previously submitted materials as needed. If a summary of the adverse event or a cover memorandum for the report is prepared by the Coordinating Center, it may be reviewed and corrected as necessary by the PI before the report is submitted to the local/central IRB.

Each expedited safety report should routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A, and any additional pertinent information recommended by the Coordinating Center or the AREDS2 Medical

Monitor. Once the report is assembled, the PI must submit the expedited safety report to the local/central IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The PI must retain a complete copy of each expedited safety report as it was submitted to the IRB, and forward a copy of each report to the Coordinating Center. The Coordinating Center will be responsible for further dissemination of expedited safety reports as described below.

5.2.1.3 Contacting the Coordinating Center

Each clinical site is assigned a Protocol Monitor from the Coordinating Center. Be sure to indicate clearly the study name and the site number when contacting the Coordinating Center. Back-up personnel and procedures exist to assure that personnel at the Coordinating Center can adequately handle urgent requests or adverse event reporting requirements.

The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, Maryland 20850
Telephone (toll-free): 866-375-9924
Fax (toll-free): 877-804-9618
Website <http://www.areds2.org>
E-mail areds2@emmes.com

5.2.2 Obligations of Study Sponsor and Coordinating Center

The NEI, or the Coordinating Center on behalf of the NEI, must immediately investigate each reported adverse event and notify the FDA (and other relevant regulatory authorities), the DSMC, and all participating investigators within 15 days of any adverse experience that is associated with the use of the study supplements and that is both *serious and unexpected*.

If the reported adverse event is an unexpected fatal or life-threatening experience associated with the use of the study supplements, the NEI must notify the FDA and the AREDS2 DSMC as soon as possible but no later than seven calendar days after the sponsor's initial receipt of the information. In order to facilitate expedited reporting of these events, or if the Principal Investigator is

unsure about the necessity of expedited reporting, the Coordinating Center must be contacted as soon as possible to collect and prepare the necessary reporting information. All serious adverse events must be reported to the Coordinating Center through AdvantageEDCSM within 24 hrs of the site becoming aware of the event. Serious adverse events not requiring expedited reporting will be summarized in annual reports to regulatory authorities and disseminated to the DSMC, study Investigators, and IRBs still active in the study.

When the Coordinating Center or NEI has determined that expedited reporting of an adverse event is required, the Protocol Monitor will be responsible for performing the following procedures and for reporting the adverse event to regulatory authorities within the required timeframes:

- A. Notify the site that expedited reporting will be required and request any additional information needed to complete an appropriate report. This may include completion or updating the information in AdvantageEDCSM and the submission of supporting documentation, laboratory reports, discharge summaries, etc. The Coordinating Center will prepare a cover memorandum for reporting of the event to regulatory authorities.
- B. When the cover memorandum, MedWatch Form FDA 3500A, and any pertinent attachments are ready, the AREDS2 Protocol Monitor will submit a copy of the completed report, by fax or courier delivery before the regulatory reporting deadline, to the following persons:
 - FDA Medical Officer as appropriate (submitted as an amendment to the applicable IND or as an IDE supplement);
 - Site PI(s) at each active participating site (who is responsible for forwarding the report to the local/central IRB);
 - Study Chair;
 - DSMC Chair and AREDS2 Medical Monitor;
 - The manufacturer of the study supplements, when appropriate;
 - The sponsor of any IND/IDE application (if not listed above).

- C. If relevant follow-up information becomes available, the Protocol Monitor will be responsible for obtaining the details from the site. This information will be reviewed by the Medical Monitor. A follow-up MedWatch form will be completed and forwarded to all parties that received the earlier serious adverse event report.
- D. The Protocol Monitor will also transmit copies of all expedited safety reports to the designated individual from any cross-referenced IND sponsors. A copy of the safety sections for annual FDA reports will be forwarded to the NEI and will be provided to the designated individual from any cross-referenced IND sponsors.

5.2.3 Adverse Events Defined

An adverse event by definition is “any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the product”. Non-serious adverse events can be collected in a routine manner using case report forms. Serious adverse events must be promptly reported to the Coordinating Center as noted above. This permits immediate investigation by the Coordinating Center and sponsor to determine the reporting requirements to regulatory authorities.

Progression or worsening of the medical condition under study, by itself, does not necessarily constitute an adverse event unless the change can be reasonably attributed to an action of the study supplements and not only to its lack of efficacy. In subjects undergoing ocular treatments for CNV, for example laser, PDT, Lucentis (ranibizumab), Avastin (bevacizumab), Macugen (pegaptanib), and any intravitreal injections of drugs including steroids, adverse events that are a consequence of that treatment are not required to be reported for this study. Also, a hospitalization for an elective or cosmetic procedure unrelated to the medical condition under study is excluded from this definition of an adverse event.

5.2.3.1 *Serious Adverse Events Defined*

A serious adverse event (SAE) is defined for this protocol as an adverse event that meets one or more of the following criteria:

- A. A death (CTCAE Grade 5 event) occurring during the study, whether or not considered treatment-related;*
- B. A life-threatening event (CTCAE Grade 4, or as defined in Section 5.2.5.4);
- C. An event requiring in-patient hospitalization or prolonged hospitalization due to the adverse event;*
- D. An adverse event resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function or structure, physical activities or quality of life;
- E. A congenital anomaly or birth defect, where exposure to the study supplements prior to conception or during pregnancy is suspected in resulting in an adverse outcome in the child;
- F. An event that otherwise required a medical or surgical intervention to preclude permanent impairment or damage (excluding unrelated elective or cosmetic procedures).

*Clinical sites will request a copy of death certificates and hospital discharge summaries for all deaths and in-patient hospitalizations that require expedited reporting by the Coordinating Center or have insufficient information to assess the event (as determined by the Medical Monitor). Additionally, staff at a third party, the University of Virginia, contracted on behalf of the AREDS2 Cardiovascular Outcome Study will request hospital discharge summaries and other medical documents for all cardiovascular- and cerebrovascular-related hospitalizations. A template Authorization for the Release of Medical Records is provided in Appendix D.

5.2.3.2 *Unexpected Events Defined*

An unexpected event is any adverse experience, the specificity or severity of which is not consistent with the current approved product labeling for the study

supplements or as described in the protocol, consent materials and the Investigator Brochure. This includes an increase in the frequency or severity of a reported adverse event that is significantly above the rates known from previous experience with the study supplements.

5.2.4 Terminology to Use for Adverse Event Descriptions

When reporting an adverse event, the event description should use the best matching terminology describing the event as found in the “Common Terminology Criteria for Adverse Events” (CTCAE, v 3.0). If an available CTCAE term fits the event well, no additional descriptors may be needed. However, necessary descriptions should be added in order to clarify the event or to place it in an appropriate context. The adverse event name should ideally be 1-3 words in length with additional description provided elsewhere on the adverse event report. A copy of the CTCAE is posted on the study web site at <http://www.areds2.org/> and is available in the study Manual of Procedures (MOP). Standardized terms from the CTCAE are used by the Coordinating Center and study sponsor to categorize events for reporting to regulatory authorities using the “Medical Dictionary for Regulatory Activities” (MedDRA). In most cases, the CTCAE terms match MedDRA coding terminology. If an appropriate term matching the adverse event cannot be found in the CTCAE and the preferred MedDRA term is unknown, the adverse event description should include a diagnosis, sign or symptom with additional information to facilitate subsequent categorization into MedDRA coding terms.

5.2.5 Grading Severity of Adverse Events

The site Investigator must grade the severity of all reported adverse events into one of four categories: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), or Grade 4 (Life-Threatening). The standardized CTCAE severity grading scales for the specific type of adverse event reported must be used when a matching CTCAE term is available. If a death occurs (equivalent to a Grade 5 event in this coding scheme) this is not coded as an adverse event by itself. The predicate

condition(s) or cause(s) of death should be recorded as the adverse event(s) of Grade 4 where the outcome is death. The highest severity grade experienced for the event should be reported to the Coordinating Center. The initial severity grading may be updated in follow-up reports if the maximum grade changes to a higher level. Specific events not described in the CTCAE that are expected to be observed or monitored during the study are listed in the Investigator's Brochure along with relevant severity grading criteria. If no reference to a standard grading scale applies or is immediately available, use the following guideline:

5.2.5.1 *Grade 1—Mild*

Transient (< 48 hours) or mild discomforts, no or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities, nonprescription or single-use prescription therapy may be employed to relieve symptoms (e.g., aspirin for simple headache, acetaminophen with codeine for post-surgical pain). Mild adverse events may be listed as expected consequences of the therapy for any given protocol, and standard supportive measures for such an expected event do not necessarily elevate the event to a higher grade.

5.2.5.2 *Grade 2—Moderate*

Mild to moderate limitation in activity, some assistance may be needed; possibly none but usually minimal intervention/therapy required, hospitalization possible.

5.2.5.3 *Grade 3—Severe*

Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely.

5.2.5.4 *Grade 4—Life-Threatening*

Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment or hospice care probable. This grade is used when the participant was, in the view of the Investigator, at substantial risk of dying at the time of the adverse event or it was suspected that use or continued use of the study supplements would have resulted in the participant's

death. (This does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.)

5.2.6 Relatedness of Event to Study Supplements

The site Principal Investigator (or an authorized study physician) must submit an attribution for the relatedness of the reported adverse event to the study supplements. The attribution should take into account both the temporal association and any known physical, physiological or toxicological information regarding the study supplements that could reasonably infer causality. Relatedness should only be considered for the study supplements and not for any standard study examination or diagnostic procedures. The four attribution categories are:

1) Definite—*Clearly related* to the study supplements.

An adverse event that follows a temporal sequence from administration of the study supplements; follows a known response pattern to study supplements; and, when appropriate to the protocol, is confirmed by improvement after stopping the study supplements (positive rechallenge; and by reappearance of the reaction after repeat exposure (positive rechallenge)); and cannot be reasonably explained by known characteristics of the participant's clinical state or by other therapies.

2) Probably—*Likely related* to the study supplements.

An adverse event that follows a reasonable temporal sequence from administration of study supplements; follows a known response pattern to the study supplements, is confirmed by improvement after rechallenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.

3) Possibly—*May be related* to the study supplements.

An adverse event that follows a reasonable temporal sequence from administration of study supplements and follows a known response pattern to the study supplements, but could have been produced by the

participants' clinical state or by other therapies.

4) Unrelated—*Clearly NOT related* to the study supplements.

An adverse event that does not follow a reasonable temporal sequence after administration of the study supplements; and most likely is explained by the participant's clinical disease state or by other therapies. In addition, a negative rechallenge to the study supplements would support an unrelated relationship.

5.3 Withdrawal Criteria

Participants may choose to withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other NIH protocols. Participants who develop an adverse reaction to the study supplements or a serious complication associated with or aggravated by continuation of study supplements may be withdrawn from the study supplement. Following study supplement discontinuation, participants will return for their originally scheduled annual visit.

5.4 Monitoring Guidelines

At a minimum, the DSMC will review the study data at the time points defined in Section 6.4.1 to identify any issues with safety or the general conduct of the study. The DSMC may recommend temporary suspension, or to close enrollment, or stop the study at any time due to safety concerns, demonstration of efficacy or lack of efficacy, or slow enrollment.

Before recommending closing enrollment or stopping the study, the DSMC will consider:

- Internal consistency of primary and secondary results.
- Distribution of baseline prognostic factors among the treatment groups.
- Consistency of primary and secondary results across clinical centers and among centers enrolling larger numbers of participants.

- Sensitivity of the results to adjust for missing data and the possible impact of missing data from missed participant visits for assessment of the primary and secondary response variables.
- Any other considerations that the DSMC may want to review.

6.0 Statistical Considerations

The primary objective of this study is to evaluate the effect of lutein/zeaxanthin and/or DHA/EPA in high supplemental doses on the progression to advanced AMD. The secondary objectives include assessing the effect of lutein/zeaxanthin and omega-3 LCPUFAs in high supplemental doses on moderate vision loss (doubling of the visual angle or the loss of 15 or more letters) and cataract and to study the effect of eliminating beta-carotene and reducing zinc in the original AREDS formulation on the progression and development of AMD and/or moderate vision loss.

6.1 Sample Size and Power

The majority of the AREDS2 participants will have at least five years of follow-up. The power considerations presented are based on 5-year AMD incidence rates. The event rates are derived from the placebo arm of the participants enrolled in the Age-Related Eye Disease Study (AREDS).

The 5-year progression rates to advanced AMD for AREDS participants with either bilateral large drusen or large drusen in one eye and advanced AMD in the second eye were 27.7% and 48.7%, respectively, for participants assigned to placebo and 22.4% and 37.5%, respectively, for participants assigned to ATS.

Weighted 5-year rates of progression were computed for the primary outcome assuming that 60% of the participants recruited will have bilateral large drusen and 40% of the participants will have large drusen in one eye and advanced AMD in the second eye. If this mix of participants was assigned to ATS, the 5-year weighted progression rate is 28.4% for advanced AMD. Assigning the same mix of participants to placebo, the 5-year weighted progression rate is 36.1% for advanced AMD.

To compute the necessary sample size, adjustment for deaths and losses to follow-up was calculated. In AREDS the mortality rate over the first five years was 6%, which will also be used as the estimated death rate for AREDS2. The losses to follow-up in AREDS were only 1.3%. It is assumed that this rate may be lower than what can be achieved in AREDS2. Although efforts will be made to meet or exceed that excellent result, a conservative estimate of a 15% loss to follow-up will be used. Using this 5-year rate for losses to follow-up and the progression rates above, 4,000 participants will provide adequate power (at least 90%) to detect a 25-percent difference between the placebo group compared with each of the treatment groups (Table 1) for progression to advanced AMD. This level of additional reduction in risk associated with lutein/zeaxanthin and/or EPA/DHA supplementation is similar to the risk reduction found with the original AREDS formulation and would be considered a clinically important further reduction in risk.

Table 1. Advanced AMD - Required Sample size per Treatment Group*

	Use original AREDS formulation	Sample Size
25% Reduction	65%	851
	85%	916
	90%	933
	95%	950
30% Reduction	65%	590
	85%	623
	90%	631
	95%	655
35% Reduction	65%	422
	85%	448
	90%	462
	95%	466

* **Progression rate: 65% use = 31.1%; 85% use = 29.6%; 90% use = 29.2%; and 95% use = 28.8%**

* Log rank test

* Two-arm comparison

* 90% power

* Bonferroni adjusted for three pairwise comparisons (Placebo compared to the three treatment groups)

* Two-sided $\alpha = 0.05$

* 15% loss to follow-up

* Accrual: 1.5 years Follow-up: 5 years

6.2 Evaluable Data

The evaluable data set will include all available data from participants who meet the eligibility criteria based on clinician evaluation and who are ultimately randomized into the study. These outcomes will be analyzed according to the treatment to which they were randomized, even if different from the treatment actually received (intent-to-treat).

6.3 Efficacy Analyses

6.3.1 Interim Analysis for Efficacy

The DSMC will review accumulating data of the study on an annual basis. For the purpose of sequential monitoring, the primary endpoint is progression to advanced AMD. An eye progresses to advanced AMD with the development of one or more of the following: geographic atrophy involving the center of the macula, retinal pigment epithelial (RPE) detachment, serous detachment of the sensory retina, subretinal hemorrhage, disciform scar, or treatment of CNV.

The following group sequential test plan for efficacy outcome describes how alpha (α) will be spent across the annual interim looks and a final look at the data. This interim analysis will be performed based on the efficacy outcome and will be unadjusted by any covariates. Interim safety analyses will be conducted at the same time as interim efficacy analyses. The annual interim looks and a final look will be based on the group sequential procedure for a single time to event outcome variable described by Lan and Lachin.⁵⁹ Their procedure is based on the alpha spending function approach of Lan and DeMets.⁶⁰ The alpha level or Type I error in a non-sequential design is assigned to one (final) analysis. In repeated interim analyses the cumulative Type I error increases with each interim evaluation. The goal of a group sequential design is to control the overall Type I error rate. Here, “overall” means accounting for interim analyses. The alpha spending function approach gives a rule for allocating some of the pre-specified Type I error to each interim analysis. This rule depends on the fraction of the total information of the trial accumulated by the time of interim analysis. When the log rank test is used to compare the survival pattern of the treatment groups, the fraction of information at an interim analysis is the fraction of the total number of events to be accrued in the entire trial. In AREDS2 the total number of events to be accrued is not known. Lan and Lachin⁵⁹ suggest estimating information in terms of participant exposure time (exposure time is the time from

randomization to end of follow-up or until an event is observed). Based on the spending function defined in terms of estimated information time, they describe the method for computation of the log rank test group sequential boundaries. Even though the estimated information fraction is used to determine the amount of overall Type I error allocated to a particular interim analysis, the actual number of events observed is used to compute the boundary.

AREDS2 has adopted a group sequential procedure by extending the Lan and Lachin⁵⁹ approach to a study with multiple time to event comparisons. The overall Type I error rate is controlled at a pre-specified level, accounting for both multiple comparisons and interim analyses. First, Bonferroni adjustment is used to distribute the (sometimes called experiment-wise) Type I error alpha among multiple comparisons. For example, if $\alpha = 0.05$ is assigned to the group of statistical tests of three comparisons, then $\alpha_3 = \alpha/3 = 0.017$ would be used to compute the boundary for each test. The spending of the fraction of overall Type I error allocated to each comparison (α_3) through interim analyses is then controlled by the alpha spending function for that comparison as mentioned above.

For the purposes of stopping guidelines for treatment efficacy the factorial design will be ignored and analyses of the three active treatment arms versus placebo will be considered, adjusting alpha levels accordingly for each analysis.

Therefore, the three comparisons to be made at each interim analysis are:

1. Progression to advanced AMD for lutein/zeaxanthin alone versus placebo
2. Progression to advanced AMD for DHA/EPA alone versus placebo
3. Progression to advanced AMD for lutein/zeaxanthin and DHA/EPA versus placebo

As the long-term effects of these nutritional supplements are not clearly understood, the study should be stopped early only if there is strong evidence of benefit or harm. The symmetric O'Brien-Fleming⁶¹ boundary is appropriate for

AREDS2 as it is very conservative (requires a large treatment effect to signal stopping) during the early analyses. The spending function, which approximates the O'Brien-Fleming boundary, will be used to monitor the efficacy of nutritional supplements.

The estimated information fraction, as defined in Lan and Lachin,⁵⁹ is the ratio of total exposure time up to the time of interim analysis and total exposure time by the end of the study. The true exposure time of the participants who have not experienced an event by the time of interim analysis is not known. For these participants the exposure time is defined as the time from randomization to last follow-up.

The amount of overall alpha (α) allocated to each comparison is $\alpha_3 = \alpha/3$. For each of the three comparisons, the amount of α_3 available for interim analysis performed at time t is $\alpha_3(t)$, where $\alpha_3(t)$ is obtained from the O'Brien-Fleming type spending function based on estimated information time. For purposes of illustration, Table 2 gives the critical values for the test statistic computed at some arbitrary information time points with overall alpha level fixed at $\alpha = 0.05$ and thus $\alpha_3 = 0.017$. In the application of this procedure, the true boundary to be computed at each time of analysis will be based on the actual number of events up to that time.

Table 2: Examples of Critical Values of the Test Statistic Computed for Progression to Advanced AMD (Each of the three active treatments versus Placebo)

Information Fraction	Lower Bound	Upper Bound	Cumulative Exit Prob.	
			MC Adj.	No Adj.*
0.35	-4.30	4.30	0.00002	0.00030
0.50	-3.55	3.55	0.00040	0.00305
0.65	-3.08	3.08	0.00220	0.01087
0.80	-2.76	2.76	0.00652	0.02442
0.90	-2.61	2.61	0.01108	0.03629
1.00	-2.48	2.48	0.01700	0.05000

* These cumulative exit probabilities correspond to upper and lower bounds (not shown) computed from the alpha=0.05 spending function.

6.3.2 Primary Efficacy Analyses

In assessing the primary efficacy outcome, participants will be assessed photographically at baseline (qualification) and annually post-randomization for the progression of AMD. The binary outcome of progression to advanced AMD (yes/no) will be analyzed in a survival model comparing each of the three active treatments to placebo. If assumptions of the Cox model are not met, for example, if there are changes in the proportional hazards during the course of the study, a generalized estimating equation approach may be used. This model will take into account the correlation between repeated outcomes of binary variables measured at each study visit.⁶²

6.3.3 Secondary Efficacy Analyses

Several secondary and tertiary outcomes will be analyzed in the same fashion as the primary efficacy outcome. Analyses of these outcomes are specified for each variable below. Analyses may be adjusted for any of the following covariates: baseline AMD status, baseline visual acuity status, participant's age, and gender.

A complete detailing of all analyses will be contained in the Statistical Analysis Plan (SAP). The following provides a summary of secondary efficacy outcomes to be analyzed:

1. Comparison of the three active treatment arms to placebo on the progression to moderate vision loss.
2. Effect of lutein/zeaxanthin and DHA/EPA on the progression of lens opacity or incidence of cataract surgery.
3. Comparison of the three active treatment arms to placebo on vision loss (such as a 10-letter loss) and moderate improvement in participants with advanced AMD.
4. Effect of eliminating beta-carotene in the original AREDS formulation on the progression and development of AMD.
5. Effect of reducing zinc in the original AREDS formulation on the progression and development of AMD.
6. Effect of eliminating beta-carotene in the original AREDS formulation on moderate vision loss.
7. Effect of reducing zinc in the original AREDS formulation on moderate vision loss.

The following provides a summary of tertiary efficacy outcomes to be analyzed:

1. Validation of the fundus photographic AMD scale developed from the Age-Related Eye Disease Study.
2. Effect of lutein/zeaxanthin and/or DHA/EPA on movement on the AREDS AMD simple clinical scale.
3. Effect of eliminating beta-carotene and/or reducing zinc on movement on the AREDS AMD simple clinical scale.
4. Effect of lutein/zeaxanthin and/or DHA/EPA on cognitive function as measured by the various instruments included in the AREDS2 Cognitive Function Telephone Battery.

5. Effect of DHA/EPA on cardiovascular morbidity and/or mortality (Cardiovascular Outcome Study).

Additional outcomes may be added during the course of the study.

6.4 Safety Analyses

6.4.1 Interim Safety Analyses

The alpha spending function approach will also be applied to sequential monitoring of mortality. Because mortality is not a study endpoint, but rather an adverse event, it will not be included among the multiple comparisons of endpoints. Considerations of multiple comparisons will apply only to three tests of mortality from the factorial design, to be made at each interim analysis:

1. Lutein/zeaxanthin alone vs. placebo
2. DHA/EPA alone vs. placebo
3. Lutein/zeaxanthin and DHA/EPA vs. placebo

An overall alpha of 0.10 and a one-sided procedure in data monitoring will be used. Each hypothesis will be separately tested by an one-sided α -spending method approximating stopping rules.

Table 3 gives the critical values for the test statistic computed at various information times. The amount of alpha allocated to each comparison is 1/3 of alpha, or $\alpha_3 = 0.033$. In the application of this procedure, the true boundary will be computed at each time of analysis, based on the actual number of deaths up to that time. Table 3 is calculated using Pocock stopping rules, not O'Brien-Fleming.

Table 3: Examples of Critical Values of the Test Statistics for Mortality Comparisons (Xanthophylls Vs. Placebo, Omega-3 LCPUFAs Vs. Placebo, Xanthophylls + Omega-3 LCPUFAs Vs. Placebo)

Information Fraction	Lower Bound	Upper Bound	Cumulative Exit Prob.
0.30	-8.0	2.21	0.01372
0.40	-8.0	2.38	0.01726
0.50	-8.0	2.39	0.02046
0.60	-8.0	2.38	0.02338
0.80	-8.0	2.29	0.02854
1.00	-8.0	2.27	0.03300

The DSMC will consider the interim analysis result as a resource to evaluate the risk and benefit of study treatment. When a stopping boundary is crossed, there will be an indication that at least one experimental treatment has an increased risk of mortality. A guideline for mortality that tests for main effects in the absence of a statistically significant interaction effect, although methodologically correct, may mask the effects of a harmful formulation. On the other hand, testing individual formulations in a factorial design increases the potential for declaring differences when in fact no difference exists (Type I error). For this reason, the monitoring plan is considered a guideline, which offers some protection against Type I error ($\alpha = 0.10$). The DSMC will consider the consistency of all data including the main effects analyses.

6.4.2 Additional Safety Analyses

In addition to the interim analyses described in the prior section, all reported adverse events will be listed by CTCAE term, frequency, severity, assessed relatedness to the study supplements, and treatment group. Toxicity will be monitored by evaluating nutritional biochemistry via blood specimens in a subset

of AREDS2 participants. Nutritional biochemistry will be evaluated at baseline and at multiple follow-up time points. Standard statistical tests using normal theory will be readily applicable for assessing these data.

7.0 Hazards and Discomforts

There is no known toxicity of lutein. Little is known about the toxicity of zeaxanthin. Supplements containing DHA and EPA may be associated with side effects such as loose stool, abdominal discomfort, and unpleasant belching. In addition, they may prolong bleeding time slightly. In AREDS there was a slight (2.5%) increase in the rate of urinary tract problems in participants who took the zinc formulation. Participants assigned to beta-carotene reported yellowing of the skin, but overall, participants reported few side effects. A meta analysis of 19 clinical trials that tested vitamin E found that high-dosage (≥ 400 IU) supplementation with vitamin E may increase all-cause mortality.⁶³ Of the 19 studies, AREDS and two other trials evaluated dosages of about 400 IU/d of vitamin E. Restricting data to these three studies, the group taking vitamin E was slightly more likely to be living after five years (801 deaths of 7,564 persons in vitamin E group and 806 deaths of 7,598 persons in the placebo group). A review of the mortality experience in AREDS showed that those taking the AREDS formulation (combination of antioxidants and zinc) had a 14% reduction in mortality risk after an average of 6.5 years of supplementation compared to placebo. No other adverse events are expected.

There are risks associated with the procedures required for participants in this study. However, these are all standard procedures that are performed as part of a normal eye examination. Some of the discomforts associated with the ocular exam include the following:

- (A) Dilating drops or anesthetic drops may sting. They can cause an allergic reaction, or if contaminated, can cause infection, but neither of these problems is likely to occur.

- (B) Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available.
- (C) In rare instances, the cornea may be scratched during use of a contact lens (used for examination purposes only and not a contact lens used to correct one's refractive error). A corneal abrasion of this sort may be painful, but it heals quickly with no lasting effects.

Fundus photography carries no risk. The camera flash may cause temporary discomfort for the participant.

8.0 Confidentiality and Access to Source Data/Documents

The investigators will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants in this study. Medical and research records should be maintained in the strictest of confidence. However, as part of the quality assurance and legal responsibilities of an investigator, the site must permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when permitted or required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress. Unless required by law, no copying of records with personally identifying information will be permitted. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. The site will normally be notified in advance of monitoring and auditing visits.

8.1 Contact Information Provided to the Coordinating Center

The AREDS2 Coordinating Center will be provided with contact information for each participant. Permission to obtain such information will be included in the Informed Consent Form. The contact information will be maintained in a secure database and will be maintained separately from the study data.

Representatives of the AREDS2 Coordinating Center will telephone participants to solicit consent to the AREDS2 Telephone Battery. If consent is given participants will complete a 30-40 minute cognitive function telephone battery every two years. In addition, phone contact from the AREDS2 Coordinating Center will be made, if necessary, to facilitate the scheduling of participants for follow-up visits.

9.0 Summary of GCP Compliance

This trial will be conducted in accordance with Good Clinical Practice (GCP) using the guidance documents and practices offered by ICH and FDA, and in accordance with the Declaration of Helsinki and the policies and procedures for the AREDS2 Coordinating Center at The EMMES Corporation. This study will also comply with the regulations 21 CFR Parts 50, 54, 56, and 312 under an IND application authorized by FDA.

9.1 Investigator Responsibilities (Form FDA-1572)

For investigations conducted under an IND, a Statement of Investigator Responsibilities (Form FDA-1572) including the names of all co-Investigators and key study personnel will be completed and signed by the Principal Investigator at each site. The general responsibilities of the Investigator as acknowledged on the Form FDA-1572 are governed under the regulations in 21 CFR Parts 50, 54, 56, and 312. All study Investigators will be required to disclose their financial interests in the study supplements or study sponsors per 21 CFR 54 – Financial Disclosure by Clinical Investigators, Subsection 4 – Certification and Disclosure Requirement. The study supplements may be consumed only in accordance with the approved protocol and under the supervision of the Investigator or a co-Investigator listed on this form. The Investigator must maintain accurate and complete study records, including records for disposition of the study supplements, and an accurate and complete record of all submissions made to and received from the IRB/IEC, including a copy of all reports and documents submitted. Adverse experiences that are reported to the FDA as IND Safety Reports or as described in Section 5.2 must be submitted promptly to the local or central IRB/IEC and the Coordinating Center. Progress reports must be submitted by the Investigator to the IRB/IEC at least once per year via the Coordinating Center. The

IRB/IEC must be promptly notified of completion or termination of the study. Within three months of study completion or termination, a final report from the Investigator must be provided to the IRB/IEC and to the sponsor via the Coordinating Center.

The curriculum vitae (CV) or a résumé for each Investigator and co-Investigator must also be supplied if named on the Form FDA-1572 [or Investigator Agreement]. This form and related CVs must be supplied to the AREDS2 Coordinating Center prior to initiating the trial at each site. When necessary due to personnel changes, updated versions of the Form FDA-1572 must be forwarded to the AREDS2 Coordinating Center and copies of all versions must be maintained in study records at each site. Any CV or résumé collected at the beginning of a study should be current, and would need to be updated during the study only if substantial changes or additions are warranted (e.g., change of position or affiliation, certifications or licensure, or significant new publications relevant to the study protocol).

9.2 Human Subjects Protection

9.2.1 Institutional Review Board or Independent Ethics Committee

Each participating institution must have an Institutional Review Board or Independent Ethics Committee (IRB/IEC) constituted and operating in accordance with the regulations under 21 CFR Part 56 and authorized by the institution to review approved materials for this trial. A list of IRB/IEC voting members, their titles or occupations, and their institutional affiliations, as well as a copy of the Assurance of Compliance, must be kept available by the institution for inspection and copying by authorized study monitors, auditors, and regulatory officials. A central IRB is available to those institutions lacking a local IRB.

9.2.2 Review of Protocol, Consent, and Recruitment Materials

The clinical protocol, consent materials and any participant recruitment materials specific to this study must be reviewed and approved by the IRB/IEC in

accordance with local procedures and 21 CFR Parts 50, 56, and 312. Any amendments to the protocol or consent materials, or any revised materials used for the recruitment of participants in this study must also be approved in advance of their use by the IRB/IEC. Before initiation of the study, the Investigator at each investigational site will develop a consent form in compliance with 21 CFR Part 50 based on standard forms prepared by the AREDS2 Coordinating Center. In this multi-center trial, the clinical protocol and consent materials must be consistent at all sites with the standard protocol and consent documents provided by the AREDS2 Coordinating Center and will be made available on the study website (www.areds2.org). Any site that requires a local version of the clinical protocol or consent documents (e.g., reformatting or certain standard text as required by the local IRB/IEC) must have those versions also approved by the AREDS2 Coordinating Center before they are placed in use.

Substantial deviations from the standard protocol and consent documents in terms of content, treatment regimens, evaluations (except for sub-studies to be performed at selected sites), reporting of results, or statements describing the risks and potential benefits to participants will not be acceptable. Written approval of the protocol and the consent form(s) must be obtained from the IRB/IEC and transmitted to the AREDS2 Coordinating Center prior to enrollment of participants at each site. Written approvals must specify which of the components (i.e., protocol, consent and/or recruitment materials) is being approved, and explicitly indicate the study title (or short title) and the protocol code number and date (and/or version number, if used) on the cover page of the protocol or any amendments. Written approvals should explicitly state the duration of the approval, or preferably the expiration date of the approval, and the date when application for continuing approval is required. In accordance with 21 CFR Part 56, a written notification by an IRB/IEC that modifications are required to secure IRB/IEC approval for the protocol, consents or recruitment materials is not considered adequate documentation of final approval, even if the modifications have been made. In such a case, it is required that the site

Principal Investigator receives written final approval from the IRB/IEC acknowledging the completion of the required modifications. At least once per year, the IRB/IEC must review and give written approval to continue the study.

9.2.3 Requirements for Training in Human Subjects Protections

Each of the key personnel for this study must provide documented evidence of having completed training in the ethical conduct of clinical studies and in the protection of human subjects. Key personnel for this purpose will include each site Principal Investigator and co-Investigator listed on the Form FDA-1572 [or Investigator Agreement] for this trial, and other study personnel (who may or may not be listed on the Form FDA-1572) directly involved with the selection, evaluation, study data management, or care and treatment of study participants. This would be expected to include the study Coordinator and/or study nurse, pharmacist, photographers, ophthalmic technician or optometric professional who perform evaluations of study variables, individuals who prepare, review or abstract study-related medical records, perform data entry, directly assist with preparation or administration of the study supplements, or who otherwise have direct communications with and/or have access to personally identifiable medical information regarding study participants. Institutional certifications may be acceptable documentation provided the training is substantially equivalent to that provided by DHHS, NIH or its various Institutes and Centers. If the participating institution does not provide such training directly, or if it is not considered acceptable to NEI or DHHS (as determined by the AREDS2 Coordinating Center or sponsor), a recommended option for participating key personnel is to complete the Internet web-based computerized training offered by the National Cancer Institute, which can be found at: <http://cme.nci.nih.gov/>. This program requires approximately 2-3 hours to complete, and a numbered certificate is issued upon successful conclusion of the training. Documentation of the training for all key study personnel must be forwarded to the AREDS2 Coordinating Center prior to study initiation and promptly upon identification of any new personnel becoming involved with the trial once it is underway. Personnel who fail to provide this

documentation will not be allowed to see AREDS2 participants until the evidence of certification is submitted to the Coordinating Center.

9.3 Data Handling and Record Keeping

The site Principal Investigator is responsible for maintaining adequate clinical records documenting the medical history, condition, and test results for each study participant at his/her site throughout the study. Source documentation may consist of written or electronic records and supporting data maintained by the Investigator and/or the institution. The case histories (anamneses) or medical records for each participant shall document that informed consent was obtained prior to participation in the study.

9.3.1 Case Report Forms

Clinical data will be keyed on electronic Case Report Forms (eCRFs) in the AdvantageEDCSM system for download to the Coordinating Center in accordance with the procedures specified in the AREDS2 Manual of Procedures (MOP). Data on eCRFs downloaded to the Coordinating Center must correspond to and be supported by source documentation maintained at the investigational site, unless the site makes direct data entry into EDC for which no other original or source documentation is maintained. In such cases, the site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Coordinating Center must carry only coded identifiers such that personally identifying information is not shared with the Coordinating Center.

9.3.2 Data Transmittal

The primary method of data transmittal to the Coordinating Center will be via the secure, internet-based electronic data capture (EDC) system (AdvantageEDCSM) maintained by The EMMES Corporation. Paper forms will be available as a back-up system in the event that the AdvantageEDCSM system is unavailable.

The current MOP and access to the AdvantageEDCSM system is available to authorized users via the Coordinating Center's Internet web site, located at <http://www.areds2.org/>. An assigned username and password are required for access. All data transfers between the investigational site and the Coordinating Center via EDC are encrypted using Secure Socket Layer (SSL) technologies to assure reliable and confidential data transfer.

9.3.3 Quality Control and Quality Assurance

The Coordinating Center maintains quality control by following standard operating procedures beginning with the data entry system and quality assurance through data quality assurance verification checks. Missing data or data anomalies identified by the Coordinating Center are communicated to the site for clarification. Following standard procedures, the Coordinating Center will perform monitoring activities, including on-site audits and periodic reviews of database entries to verify and assure the quality of recorded clinical data.

9.4 Protocol Amendments

The Investigator will not modify the protocol or alter the research activity without notifying the IRB/IEC and the Coordinating Center. Except for the emergency provisions in 21 CFR 312, where deviations from the protocol may be necessary to eliminate apparent immediate hazards to the study participants, prior notification to and approval from the Coordinating Center and the IRB/IEC is required for deviations from the protocol. Protocol modifications that have an impact on participant safety, the scientific soundness or validity of the investigation, or the rights and welfare of study participants must be submitted in advance for approval by the Coordinating Center and approved by the IRB/IEC prior to implementation. The Coordinating Center will forward authorized protocol amendments and related documentation to all the participating sites, the DSMC, FDA, and study sponsors, as appropriate.

9.5 Monitoring Plan

The Coordinating Center will follow standard operating procedures for monitoring this study in accordance with GCP recommendations and FDA regulatory requirements. Any site not meeting the minimum requirements to initiate the trial will be notified in writing of the deficiencies and permitted a reasonable opportunity to rectify deficient conditions. The same holds true for any site that has administrative, procedural or data quality deficiencies that require correction in order to: (a) comply with regulatory requirements; (b) the protocol; and/or (c) meet the requirements of the sponsor and the AREDS2 Coordinating Center. The inability of the site to rectify seriously deficient conditions in a timely manner or to maintain compliance with regulatory requirements may be cause for termination of study activities, closure of the investigational site, and notification of that decision to the site's IRB/IEC and other regulatory authorities as appropriate.

9.5.1 Planned Site Visits

Participating sites will have at minimum one routine monitoring visit during the course of the study. The visit(s) will be conducted by experienced monitoring personnel. Additional monitoring visits may be performed for cause or if the volume of information to be reviewed cannot be completed in a single visit. If deemed necessary, a pre-study qualification visit may be performed for participating centers not recently visited by Coordinating Center monitors to determine if the site has appropriate facilities, adequate participant population, and properly trained and experienced staff required for study conduct.

Independent data audit visits may be conducted separately from the routine site monitoring visits. These audits will be authorized by the AREDS2 Coordinating Center or by the AREDS2 Operations Committee. Every effort will be made to schedule study visits well in advance so that necessary site staff and appropriate records will be available during the monitoring visit.

9.5.2 Items Reviewed at Site Visits

Each monitoring visit will utilize a standardized checklist of elements to be reviewed at the site, tailored to the specific requirements of this study. Monitors will routinely review the participating site staff roster; study administrative documents; required regulatory documentation; status of IRB/IEC approvals; changes or actions taken since any previous visit; participant recruitment status, screening, enrollment, and follow-up visit records; documentation of informed consent for each participant; review of adverse events; study supplement storage conditions, inventory, expiration dates and accountability; biological specimens or photographs awaiting transport or assessment; outstanding data clarifications and a review of selected data elements against source documentation. Site visits will follow standard Coordinating Center procedures and a report will be prepared for study records.

9.5.3 Regulatory Binder(s)

Each site will maintain a confidential regulatory binder that contains site-specific and study-wide documentation. The regulatory binder does not contain clinical records, CRFs, or other source documentation regarding individual participants. The site Principal Investigator is required to maintain this documentation and make it available for review by authorized study monitors, auditors and regulatory authorities. Both current and outdated study documents must be maintained. Older versions of documents may be stored elsewhere in a secure location, provided a reference to the actual storage location remains in the binder. If the binder contents become voluminous, multiple volumes may be maintained. Two separate parts of the regulatory binder are to be maintained whenever the study supplements are stored and dispensed from a location not under the control of the site Principal Investigator. The site Principal Investigator or Study Coordinator maintains the first part and the pharmacist or other person responsible for storage and inventory control of the study supplements maintains the second part. Contents of the regulatory binder(s) must include the following sections (the order of which may vary), and may be supplemented with additional

dividers if necessary. Any empty or unused sections should contain a document acknowledging this status.

AREDS2 Regulatory Binder

Investigator Documents

- Curriculum vitae

- Professional licenses for investigators

- Form FDA-1572

- Financial Disclosures

IRB Documents

- IRB submissions

- IRB/IEC approved consent form

- IRB/IEC approved recruitment materials

- IRB/IEC Compliance letter and roster

Referring Physician's Brochure

Investigator's Brochure

Protocol

- Clinical Protocol

- Amendments

- Investigator Statement of Approval (Protocol signature page)

Summary Safety Reports

- IND summary reports from other sites

Staff Materials

- Site Authorized Representatives Log

- Certifications for human subject protection training

- Protocol-specific training/certifications

Study Supplement Accountability

- Manifests of inventory received

Monitoring

- Site Monitoring Log

- Site Monitoring Reports

Correspondence

- Correspondence with sponsor/manufacturer/Coordinating Center

- Numbered Memo Checklist

- Other correspondence

- Miscellaneous documentation

9.5.4 Clinical Data

Selected clinical data may be reviewed at monitoring visits according to a plan prepared prior to the visit by the Protocol Monitor. Typically, a selection of participant data elements are chosen, emphasizing those elements considered primary analysis variables and other key elements including participant identifier codes and safety variables. An element-by-element comparison to source documentation will be performed to determine the accuracy of the data elements as they appear in the Coordinating Center's study databases. Discrepancies will be recorded and the list of discrepancies will be reported to the site Principal Investigator and/or Coordinator. In some cases, an audit of as much as 100% of study data elements may be performed for one or more participant records. Depending on the observed data discrepancy rate (number of discrepancies / total number of data elements reviewed), additional clinical data may be scrutinized at a more or less rigorous level than the initial plan, either during the same visit or at subsequent monitoring visits. Higher discrepancy rates will cause an increased level of review. All observed discrepancies will be corrected if possible during the monitoring visit. Any outstanding discrepancies may be resolved later and reported to the Coordinating Center in accordance with standard procedures.

9.5.5 Monitoring Visit Reports

Protocol Monitors will prepare written reports for each monitoring visit according to standard procedures. Reports will summarize the site administrative and regulatory status, detail data discrepancies observed and corrected, and list outstanding deficiencies that still require correction.

9.5.6 Routine Communications

Communications between the investigational site and the Coordinating Center will be maintained through regular telephone and e-mail contacts between the Coordinating Center Protocol Monitor and the site Principal Investigator and/or Coordinator. A log of substantive communications must be maintained both at the site and at the Coordinating Center, containing the date and a summary of communications where instructions are given or received, an interpretation of protocol requirements is made, recommendations for corrections to study documentation are made, or where the reporting of possible adverse events is discussed.

9.5.7 Data Element Reviews at the Coordinating Center

Through the AdvantageEDCSM and internal proprietary systems, the Coordinating Center Protocol Monitor has access to all submitted data elements and an automated system to alert the Protocol Monitor to missing CRFs, data anomalies, and adverse event reports. The Coordinating Center will prepare routine reports of study data for review by the DSMC, the Medical Monitor(s) and sponsor, and will promptly prepare ad hoc reports as needed for the immediate review of potential adverse events reported to the Coordinating Center or discovered by Coordinating Center staff during monitoring activities.

9.6 Retention of Records

The site Principal Investigator is responsible for maintaining intact study records for a period of at least two years following the date of approval of a marketing application for the test article with the indication for which this study is conducted. If no application is filed or approved for that indication, study records will be maintained until two years after the investigation is discontinued and FDA is notified. Local policies for records retention may require longer periods, or the NEI may request a longer retention period.

The NEI should inform the Investigator/institution in writing when trial-related records are no longer needed.

10.0 Publication Policy

Participating investigators will be required to sign agreements that include confidentiality and publication clauses to assure that confidential and proprietary information is controlled and protected. The Coordinating Center must receive these signed agreements prior to study initiation at each site. While publication of clinic study results will be encouraged, the publication policy will include a statement regarding both the NEI's and the DSMC's right to preview, recommend corrections, and if necessary, temporarily embargo publications or presentations regarding data obtained during the study. This review requirement is in place to ensure coordination of study data publication and adequate review of data for publication against the study database for accuracy. At the conclusion of the study, investigators and staff who contribute substantially to the study may be invited to participate in manuscript preparation and publication.

11.0 Financing and Insurance

The Coordinating Center is funded through a contract with the NEI, which has committed funds and effort in support of this trial. The AREDS2 Coordinating Center, operated by The EMMES Corporation, 401 N. Washington Street, Suite 700, Rockville, Maryland, 20850, is responsible for statistical design and analysis, general study management, data collection and data management, clinical study monitoring, assistance with regulatory submissions, and data quality assurance. Adequate documentation regarding financial agreements must be received by the Coordinating Center prior to initiating the study at each site.

Each participating institution must have adequate liability insurance coverage to satisfy their institutional and any federal requirements. Neither NEI, nor the AREDS2 Coordinating Center, The EMMES Corporation, can indemnify the investigational site, individual investigators or other study personnel participating in the trial, or provide

insurance for any entity. It is the site's responsibility to obtain appropriate insurance for its institution and study staff.

12.0 Certifications and Training Requirements

The Study Chairperson will appoint a Training and Certification Committee to develop a training program and establish certification criteria.

12.1 Refraction and Visual Acuity

Specific certification in NEI/ETDRS techniques for refraction and visual acuity determinations is required for this study. Certification involves a practicum and testing in both competent use of the technique and proper recording of the data. The methodology is described in detail in the AREDS2 Refraction and Visual Acuity Training Manual. Each person (e.g., physician, optometry professional, ophthalmic technician and/or nurse) that performs these determinations on study participants must be certified. If necessary, training and certification in the NEI/ETDRS methods can be provided prior to study initiation. The Coordinating Center must review and approve any training or certifications not conducted by EMMES staff.

12.2 Photographic Procedures Certification

Specific certification is required in techniques for modified 3-standard field color fundus photography. Certification will be provided by the AREDS2 Reading Center for all study staff performing these examinations prior to enrollment of participants into the study. Refer to the AREDS2 Fundus Photograph Reading Center MOP.

12.3 Professional Licensure

Physicians must provide evidence of current medical licensure applicable to the study location(s) if they are practicing medicine and undertake to diagnose and/or treat participants (including administration of the study supplements) in this study. A physician who is a site Principal Investigator must also provide satisfactory evidence of ophthalmology training before study initiation.

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Appendix A. Information for Participants Booklet

Note to Protocol readers: The text contained in this booklet is considered final and has received AREDS2 DSMC and study leadership approval. No modifications will be accepted. Hard copies of this material in a booklet form will be provided by the Coordinating Center to each Clinical Center pursuant to IRB approval.

ABOUT THIS BOOKLET

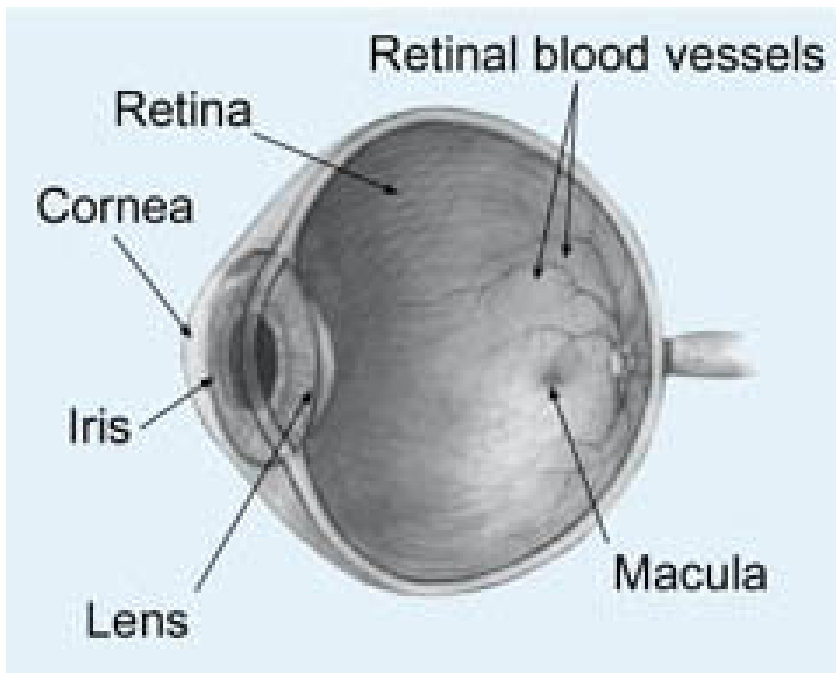
This booklet is for people thinking about taking part in The Age-Related Eye Disease Study 2 (AREDS2): A Multi-center, Randomized Trial of Lutein, Zeaxanthin, and Omega-3 Long-Chain Polyunsaturated Fatty Acids (Docosahexaenoic acid [DHA] and Eicosapentaenoic acid [EPA]) in Age-Related Macular Degeneration. The main goal of this research study is to see whether certain pills can help to prevent or slow macular degeneration. The study will also look at whether reducing or eliminating certain vitamins and minerals from a previous nutritional pill that slowed macular degeneration in people at risk for the advance stages of the disease will work as well as the original supplement did. Your doctor's exam of your eyes show you are at risk for age-related macular degeneration or you already have the advanced form of the disease in one eye.

Before you decide to take part in AREDS2, read this booklet carefully. Discuss this study with your doctors, family and friends. We will answer any questions you have.

Our medical center is one of up to 100 clinical centers in the United States participating in this study. About 4,000 people will take part in AREDS2. The study is supported by the National Eye Institute, part of the federal government's National Institutes of Health.

WHAT IS AGE-RELATED MACULAR DEGENERATION?

Age-related macular degeneration (AMD) is a disease that blurs the sharp, central vision you need for “straight-ahead” activities such as reading, sewing, and driving. AMD affects the macula, the part of the eye that allows you to see fine detail (See diagram). The macula is located in the center of the retina, the light-sensitive tissue at the back of the eye. The retina instantly converts light, or an image, into electrical impulses. The retina then sends these impulses, or nerve signals, to the brain.



In some cases, AMD advances so slowly that people notice little change in their vision. In others, the disease progresses faster and may lead to a loss of vision in both eyes. AMD is the leading cause of vision loss in Americans 60 years of age and older.

The most common types of AMD changes are tiny yellowish spots beneath the retina called drusen. Drusen can be seen by your doctor and on photographs of your eyes. Most people over the age of 60 have a few small drusen. Many large drusen may indicate AMD is present, but vision may still be nearly normal.

There are two main types of AMD. About 85 to 90 percent of people with AMD have the “dry” type in which the outer layers of the retina slowly break down. This process may lead to a gradual blurring of vision that people may notice when they try to read.

Dry AMD has three stages:

Early AMD. People with early AMD have either several small drusen or a few medium-sized drusen. At this stage, there are no symptoms and no vision loss.

Intermediate AMD. People with intermediate AMD have either many medium-sized drusen or large drusen. Some people have blurred central vision. More light may be needed for reading and other tasks.

Advanced Dry AMD. In addition to drusen, people with advanced dry AMD have a breakdown of light-sensitive cells and supporting tissue in the central retinal area. You may have difficulty reading or recognizing faces unless they are very close to you.

Once dry AMD reaches the advanced stage, no treatment is available to prevent vision loss. However, early treatment can delay or possibly prevent people from progressing to the advanced stage.

Vision loss tends to be quicker and more severe in the second type of AMD, the “wet” form. People find that straight lines appear crooked and distorted, an effect caused by abnormal blood vessels growing under the retina and leaking fluid and blood, lifting up the retina. The wet form of AMD can be treated with laser surgery, photodynamic therapy, and injections of drug into the eye. None of these treatments is a cure for wet AMD.

Macular degeneration is one of the most common causes of vision loss in older adults. It does not, by itself, result in total blindness. Most people with severe vision loss from macular degeneration can be assisted by low-vision aids for reading and can move about independently and continue activities that do not require detailed vision.

WHY AREDS2?

The major goal of AREDS2 is to learn what role nutritional pills with lutein and zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), play in preventing or slowing the development of AMD. Lutein and zeaxanthin are carotenoids, yellow and orange pigments found in many fruits and vegetables including corn, sweet potatoes, carrots, squash, tomatoes and dark leafy greens such as kale, spinach and collards. Lutein and zeaxanthin may play a role in eye health. Both are present in high levels in the retina and lens of the eye. DHA and EPA are long-chain polyunsaturated fatty acids found in fish oil. DHA is essential for normal brain and eye development. DHA can be found in high amounts in the rods and cones of the eye. The rods and cones receive and process information we use to see.

An additional goal of the study is to learn whether forms of the AREDS nutritional supplement with reduced zinc and/or no beta-carotene will work as well as the original pill in reducing the risk of progression to advanced AMD.

People who have either of the following may be eligible for AREDS2:

- AMD in an intermediate stage (large drusen) in both eyes
- AMD in an intermediate stage (large drusen) in one eye and AMD in an advanced stage in the second eye.

RANDOMIZATION AND NUTRITIONAL SUPPLEMENTATION

Scientific studies are often designed so that one group of participants receives a “standard” or common treatment for a disease and another group receives a new and promising but unproven treatment, which can then be compared with the standard. A participant is assigned to one treatment or the other by a process called randomization. Randomization is like flipping a coin, so that the treatment the participant receives is selected by chance.

In AREDS2 the study pills will be compared to a placebo, a similar-looking pill with inactive or “dummy” ingredients, in a randomized study. Participants will be divided into four groups – one will receive lutein/zeaxanthin and a placebo that resembles the DHA/EPA pill, a second will receive DHA/EPA and a placebo that resembles the lutein/zeaxanthin pill, a third will receive lutein/zeaxanthin and DHA/EPA, and the fourth will receive placebos resembling the lutein/zeaxanthin pills and the DHA/EPA pills. By comparing the first three groups with the placebo-only group, we can see if there are benefits or risks to the treatment. That is, do the eyes of people taking the study pills look better or worse than the eyes of people who are taking the “dummy” pills? Neither you nor the clinic staff will know which type of pills you are taking. The purposes of this decision are to make sure people continue to act as they do in normal life and that the staff working on the study treats all people equally. This decision will allow us to make stronger conclusions about our findings.

People in this study are at a high risk of having advanced AMD. The first AREDS study found that taking pills with high doses of vitamins and zinc reduced the risk of having advanced AMD. In AREDS2 you can be in a sub-study that will see whether similar pills with either reduced zinc and/or no beta carotene work as well as the first formulation studied in AREDS. Participants in this sub-study will be divided into four groups – one will receive the original AREDS formulation, a second will receive the AREDS formulation with reduced zinc, a third will receive the AREDS formulation with no beta carotene, and a fourth will receive the AREDS formulation with reduced zinc and no beta carotene.

The AREDS2 researchers will watch all participants for possible side effects (harmful effects) of the pills. The Data and Safety Monitoring Committee, a special group of medical and nutrition experts, will review the results regularly. As soon as we learn whether or not the treatments are of benefit, we will give the information to all participants in the study. The results will also be published so that doctors and other people outside the study can benefit from the information.

WHAT DOSES WILL BE USED?

The lutein/zeaxanthin tablet will contain 10 milligrams of lutein and 2 milligrams of zeaxanthin. There is no recommended daily allowance (RDA) for lutein and zeaxanthin. The RDA is an amount determined by the Food and Nutrition Board of the National Research Council, a part of the National Academy of Science. Average lutein/zeaxanthin intake ranges for most people are 2 to 4 milligrams per day.

The two DHA/EPA capsules will contain a total of 1 gram of DHA (approximately 350 milligrams)/EPA (approximately 650 milligrams). Because DHA and EPA are not considered essential to your diet, there is no RDA for DHA and EPA. In the United States, the average person eats an estimated amount of 130 milligrams (0.13 grams) of DHA and EPA each day.

A summary of the daily doses for the study pills is provided below:

Randomization Group	Daily doses
Placebo	Placebo-lutein/zeaxanthin (1 tablet) Placebo-DHA/EPA (2 soft-gel capsules)
Lutein/zeaxanthin only	10 milligrams lutein and 2 milligrams zeaxanthin (1 tablet) Placebo-DHA/EPA (2 soft-gel capsules)
Omega-3 long-chain polyunsaturated fatty acids	Placebo-lutein/zeaxanthin (1 tablet) 350 milligrams DHA and 650 milligrams EPA (2 soft-gel capsules)
Lutein/zeaxanthin & Omega-3 long-chain polyunsaturated fatty acids	10 milligrams lutein and 2 milligrams zeaxanthin (1 tablet) 350 milligrams DHA and 650 milligrams EPA (2 soft-gel capsules)

If you also agree to be in the sub-study looking at other formulations of the first AREDS supplement, you will be randomized to a vitamin and mineral supplement (two soft-gel capsules each day) containing the following nutrients:

Randomization Group	Amount
AREDS Formulation	Vitamin C, 500 mg Vitamin E, 400 IU Beta-carotene, 15 mg Zinc, 80 mg Copper, 2 mg
AREDS Formulation without beta-carotene	Vitamin C, 500 mg Vitamin E, 400 IU Zinc, 80 mg Copper, 2 mg
AREDS Formulation with reduced zinc	Vitamin C, 500 mg Vitamin E, 400 IU Beta-carotene, 15 mg Zinc, 25 mg Copper, 2 mg
AREDS Formulation without beta-carotene and reduced zinc	Vitamin C, 500 mg Vitamin E, 400 IU Zinc, 25 mg Copper, 2 mg

Use of other vitamin and mineral supplements

Doctors and nutritionists generally agree that supplements containing vitamins and/or minerals are not necessary for healthy people who eat a wide variety of foods. If you are not taking multivitamins, we prefer that you continue not taking any. If you are taking a supplement containing any of the AREDS2 nutrients and wish to continue, we ask that you take Centrum Silver[®]. Centrum Silver[®] is a multivitamin and mineral

supplement. We will provide this supplement free of charge to take along with your study pills. We ask that you take this multivitamin instead of the pills or multivitamins that you normally take at home so that we know what total doses you are taking. Because of the high doses of nutrients you will be taking in this study, you should not take any other pills that have lutein/zeaxanthin, DHA/EPA, beta-carotene, vitamins A, C or E, or zinc.

WHAT ARE THE POSSIBLE SIDE EFFECTS?

Your research study tablets and capsules may have higher amounts of nutrients than the RDA or what you get from foods. Nutritionists and doctors have agreed that the AREDS2 doses are not likely to have any serious harmful effects. However, side effects are possible. For example, several research studies have found that cigarette smokers should not take high amounts of beta-carotene. **Because of this chance for harmful effects, smokers (current or former smokers who quit within the last year) who agree to take an AREDS-type supplement will only receive one of the two types that do not contain beta-carotene.**

Since we cannot be sure if you will have a possible side effect from the study nutrients, at each study visit and phone call we will ask you about side effects you may have experienced. A review of the potential side effects of the research study nutrients is provided below.

Lutein/zeaxanthin. There are no proven harmful side effects from taking lutein or zeaxanthin tablets. They are considered safe with possible minor side effects, such as headache and difficulty swallowing tablets.

Omega-3 Long-Chain Polyunsaturated Fatty Acids (DHA/EPA). The DHA/EPA capsules are considered safe with possible minor side effects, such as loose stool, stomach discomfort, and unpleasant belching. In one study very long bleeding times

and increased numbers of stroke were found in people that took more than 6 times the dose of EPA + DHA being used in AREDS2.

A review of the potential side effects of each of the vitamins and minerals, which may be in your AREDS formulation capsule, is provided below.

Vitamin C. No side effects are known for AREDS2 dosage level of vitamin C. People who have had kidney stones or hemochromatosis (an iron disorder) should not take this large dose and will not be eligible to take part in the study.

Vitamin E. Side effects of high doses of vitamin E are rare and unlikely to occur among people in this study. The possible side effects include extreme fatigue, muscle weakness, blurry vision, and decreased thyroid-gland function. In people who do not have enough vitamin K, high doses of vitamin E may slow the time it takes for blood to clot. If you are taking prescription blood-thinning medications, check with your medical doctor.

A review study published in 2005 found that people taking a “high dosage” of vitamin E pills [400 International Units (IU) or more] had a greater chance of death than those who did not. This review included 19 studies that tested vitamin E. AREDS was one of the studies included in the review. Three studies, including AREDS, evaluated a vitamin E dose of 400 IU per day. In a review of these three studies, the group taking vitamin E was slightly more likely to be living after 5 years (801 deaths of 7,564 persons in the vitamin E group and 806 deaths of 7,598 persons in the placebo group). In a review of the AREDS data, people taking the AREDS formulation of vitamins and zinc were 14% less likely to die after 6.5 years of supplementation compared to the placebo group.

Beta-carotene. In doses much higher than the study dosage, some people find that their skin turns yellowish. The skin returns to a normal color when the dose is lowered. No problems are expected at the dosage to be used in this study. The effect on lung cancer of beta-carotene at a somewhat higher dose than used in this study was also

tested in 29,000 male cigarette smokers. The study found no benefits and an increase in lung cancer for people taking beta-carotene. The number of new lung cancer cases per 1,000 smokers per year was about 6 for those taking beta-carotene and about 5 for those not taking beta-carotene. There was also a somewhat smaller increase in the chance of heart disease and of death in these smokers taking beta-carotene. People who currently smoke cigarettes or use tobacco products or have had lung cancer will not be given an AREDS2 pill containing beta-carotene.

Zinc. A lack of copper leading to anemia (not enough oxygen flowing in the blood) has been reported when high levels of zinc are taken. For this reason, the AREDS2 tablets and capsules include a small amount of copper. We expect that this precaution will prevent anemia. Decreased amounts of high-density lipoproteins (HDL, the beneficial or “good” part of cholesterol) in the blood have been found in people who take about twice the dose of zinc we will be using. Sometimes zinc can cause stomach upset, but we have chosen a form that is less likely to do this. A study reported that there was a slight increase in the rate of urinary tract problems in people who took doses of zinc similar to the study pills.

Making sure the supplements are safe

Because we want to be sure that these are safe doses, we will be asking you about possible side effects during each study visit and phone call. In addition, every year several of our clinical centers will check the blood of some participants for levels of cholesterol, lutein, zeaxanthin, fatty acids, vitamin E, beta-carotene, and zinc. The amount of blood taken from those participants will be about 4.2 teaspoonfuls.

NUTRITIONAL BIOCHEMISTRY STUDY

If your blood is drawn for the Nutritional Biochemistry Study, there may be some redness or slight bruising at the site used to obtain your blood. There are no other

expected risks or consequences of participation in this study. There are no direct benefits to participation in the Nutritional Biochemistry Study; however, your participation may enable us to learn more about the possible relationship of the study pills and age related eye disease. This knowledge may allow us to develop the means to prevent these diseases in the future.

WHAT DOES THE STUDY EXPECT FROM PARTICIPANTS?

We expect you to visit the clinic for two appointments in the first three months so that we can assess your eligibility to take part in the study. After that, if you are eligible, we will contact you by telephone after another three and six months to obtain information on any side effects you may have experienced. You will then visit your clinic at least one year after your initial appointment. After that, you will come in for appointments one time each year for the remainder of the study (until 2012). Every six months in between study visits you will receive a phone call to ask about any side effects.

At your first visit, called the Qualification Visit, you will first undergo the informed consent process. This process consists of conversations between you and the research team. The research team will provide a summary of the study (including its purpose, the treatment procedures and schedule, and potential risks and benefits) and explain your rights as a participant. If you then decide to enter the study, you will give your official consent by signing the informed consent form. An informed consent form is a document that you sign to participate in a clinical study. You should not sign this document until you feel you have achieved an understanding of the relevant medical facts and the risks involved in the study.

At this visit you will have an eye exam, and we will photograph your eyes. If we find that you qualify, we will give you a trial supply of placebo pills and ask you to take one tablet and two soft-gel capsules with breakfast each day for one month. You will also be given the regular form of the AREDS-type supplement and asked to take the two soft-gel capsules each day (one capsule in the morning with food and one capsule in the

evening with food) for one month. If you are a smoker or a former smoker who has smoked during the past year, you will not receive these extra AREDS-type supplements during this qualification period, but will have the chance to take certain forms of the AREDS pills at a later time if you are eligible for the study. We are asking participants to take the placebo or dummy supply of tablets and capsules to determine how well you accept daily pills.

When we give you the placebo supply of tablets and capsules, we will ask you to stop taking any other pills containing lutein, zeaxanthin, DHA or EPA.

You will be asked to return to the clinic for your second visit, the Randomization Visit, one to three months after your first visit. At this visit, we will check your vision and examine your eyes. If you fully qualify for the study, we will go over some additional study information and ask you to sign another informed consent form.

Because the study will monitor major illnesses the participants may develop, we will ask you to sign a medical release form. This will allow us to request medical information from your doctor should you have a surgical procedure or medical treatments either in the hospital or in an outpatient facility during the course of the study.

The computer will then randomly place you in one of the study groups described previously:

- lutein/zeaxanthin + placebo DHA/EPA
- DHA/EPA + placebo lutein/zeaxanthin
- lutein/zeaxanthin + DHA/EPA, or
- placebo lutein/zeaxanthin + placebo DHA/EPA.

We will give you your supply of pills and ask you to take one tablet and two soft-gel capsules every morning.

We will also ask you whether you are interested in being randomized to take the AREDS-type formulation. If you agree to participate in the second part of the study, which evaluates the different versions of the AREDS formulation, you will also be randomly placed into a second study group:

- AREDS formulation
- AREDS formulation with no beta-carotene
- AREDS formulation with reduced zinc
- AREDS formulation with no beta-carotene and reduced zinc.

If you are a smoker, you will be given the AREDS pill with no beta-carotene or the AREDS pill with no beta-carotene and reduced zinc. We will give you this second supply of pills and ask you to take these two soft-gel capsules daily (one capsule in the morning with food and one capsule in the evening with food).

If you do not want to be in the second randomized study, but do want to take an AREDS pill, we will provide you the original AREDS formulation while you are in AREDS2. If you are a current smoker or a former smoker who quit within the last year, you will **not** be provided the AREDS formulation because it contains beta-carotene. We will ask that you stop taking any supplements containing vitamins C, E, beta-carotene, or zinc at that time. If you are now taking a multivitamin tablet with or without minerals and wish to continue taking one, we will give you a supply of Centrum Silver[®] to take instead.

Some of your AREDS2 tests will vary from visit to visit, but other tests will always stay the same. Each time you come to the clinic we will dilate your eyes, do a complete eye exam, and ask if there have been changes in your eyes or general health since your last visit. Every time you come for a visit, we will check your vision to see if there are any changes from the previous visit. We may do a “refraction” to see if we can improve your vision with different lenses. We will place drops in your eyes to dilate your pupil. We will also take photographs of the retinas of your eyes at the beginning of the study and about once a year after that. The bright flashes used to take the photographs may temporarily dazzle your vision, but are not painful and cause no damage.

From time to time we will ask you to complete questionnaires on various topics, such as your general health, cognitive function, the foods you eat, or how well you are doing in remembering to take the tablets. We will always answer any questions you have about the study or about your eyes. It is important for you to come for every visit.

WHAT ARE THE RISKS AND BENEFITS?

Risks

We believe that the risks to participants in the study are small. You have already read about the possible side effects of the study pills. Should you have any signs or discomforts that you believe could be side effects as a result of taking the study pills, then stop taking them immediately and call the Clinical Director or the Clinic Coordinator at your AREDS2 Clinical Center.

The risk and discomforts of eye exams are similar to those of eye exams you may have had in the past. For example,

- The eye drops may sting when they are first put into your eyes. The drops could cause an allergic reaction, and if they are contaminated, they could cause an infection. This problem is rare.
- Dilating drops can cause a sudden increase in pressure (acute glaucoma) in eyes that are already likely to develop this condition. This reaction is rare, and if it happens, immediate treatment is available. We will always look at your eyes before giving you the drops to judge whether you are at risk for acute glaucoma. We will advise you of any increased risk.
- Taking photographs of your eyes may cause temporary discomfort.

Benefits

The study provides you with an opportunity to learn more about your own eyes and eye diseases while you contribute to medical knowledge. We hope that what we learn about macular degeneration and cataract during the study will help those who are at risk of developing these diseases and those who may develop them in the future.

In addition, the study requires a high standard of care and follow-up that will be monitored closely. Participants will learn about study results as soon as they are available and will have the first opportunity to benefit from them.

Appendix B. Template Informed Consent Forms

First Informed Consent

The Age-Related Eye Disease Study 2 (AREDS2): A Multi-center, Randomized Trial of Lutein, Zeaxanthin, and Omega-3 Long-Chain Polyunsaturated Fatty Acids (Docosahexaenoic acid [DHA] and Eicosapentaenoic acid [EPA]) in Age-Related Macular Degeneration

Consent and Authorization to be a Research Subject

Introduction and Purpose

This consent form describes the research study and your role as a participant. In AREDS2 your ophthalmologist will become, in addition, a research investigator and you will become a study participant.

In addition to this consent, there is a booklet that provides information in a different format. Please feel free to take these documents and think about participation. Please read this form carefully. Do not hesitate to ask anything about the information provided. Your doctor or nurse will describe the study and answer your questions. We expect you to be in this phase of the study, the Qualification period, for no more than three months. Approximately [insert number] persons at [Name of Institution] and a total of 4,000 participants in the United States will be enrolled in the study.

It is important that you know the following:

1. Your participation in this study is entirely voluntary, and you may decide to stop or withdraw from this study even after signing this consent.
2. You may choose not to take part in the study and will not lose any benefits to which you are otherwise entitled.
3. You will not receive any monetary compensation for participation.

4. You may receive no benefit from taking part in the study. The study may give us knowledge that will help people in the future.
5. There is no cost to you for participating in this study.
6. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they want to receive. If you have such beliefs, please discuss them with your clinic staff before you agree to take part in the study.
7. There are no monetary costs to you or your insurer for activities performed as a part of this study.

Procedures – Qualification Visit

If you consent to be in the study, the staff will ask you questions about your medical and vision history, check your vision, take pictures or photographs of your eyes, and have a doctor examine your eyes after you are given some drops to dilate your eyes. If you match the criteria of the study, you will receive a sample of trial placebo supplements, and you will take one tablet and two soft gel capsules every day for one month. If you are not a smoker or if you are a former smoker who has not smoked during the last year, you will also receive a sample of AREDS pills, and you will take these two soft gel capsules every day for one month. We expect that your Qualification Visit will last 3 to 4 hours.

Risks

We believe that the risks to participants in the study are small. You should have read about the possible side effects of the study pills and discomfort from photography and dilating drops in the Information for Participants Booklet.

Benefits

The study provides you with an opportunity to learn more about your own eyes and eye diseases while you add to medical knowledge that may help others.

Alternatives

There is no alternative treatment for drusen. Persons with large drusen who are at risk for advanced age-related macular degeneration may want to speak with an ophthalmologist about taking the AREDS I supplement – Ocuvite PreserVision, which is available as an over-the-counter product in drug stores and many retail chains.

Freedom to Withdraw From the Study

You can stop or withdraw from this study at any time without losing any of the benefits or standard of care treatment to which you may be entitled.

Participant Safety

- Before a study begins, researchers must get approval from their Institutional Review Board (IRB), an advisory group that makes sure a study is designed to protect participant safety.
- During a study visit, doctors will closely watch you to see if you are having any side effects. All the results from your tests and exams are carefully recorded and reviewed. Clinic staff will tell you of any abnormal findings discovered as a result of the study and that may affect your standard of care. It will be up to you to decide whether to follow-up on any findings with your personal doctors.

Participation is Voluntary

Your participation in this research study is voluntary. If you refuse to participate or stop your participation, this will not harm or prejudice your future relationship with your study doctor. Your participation may be stopped by your study doctor or by the study sponsor without your consent. Your study doctor may base such a judgment on events involving yourself or other participants enrolled in the study. We may learn new things during the study that you may need to know. We can also learn things that may make you want to stop participating in the study. If so, you (or your legally appointed representative) will be notified about any new information.

Confidentiality

Your study records (study file) are just like your medical records, which contain information that is confidential and private. You and your health care team will have access to your records. The Federal Privacy Act protects the confidentiality of your study medical records. However, you should know that the Act allows release of some information from your medical records without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, the sponsor, or other authorized people. The above parties may look at your medical records so that they can see if the data are correct and also determine if federal regulations are being followed. Your study data are sent to the Coordinating Center at The EMMES Corporation located in Rockville, Maryland. You are identified only by a study number and your initials.

When results of a study are reported in medical journals or at scientific meetings, the people who took part in the study are not named nor identified. In most cases, any information about your research involvement will not be released without your written permission. However, if you sign a release of information form, for example, for an insurance company or private doctor, information from your medical record will be given

to your insurance company in this example. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

Policy Regarding Research-Related Injuries.

If you are injured during this research, you will not be reimbursed automatically for medical care or receive other compensation from the federal government or [this Clinical Center Name]. You should notify the Clinical Center Principal Investigator [PI Name] if you believe any injury has occurred.

Payments

Participants are not paid for taking part in this research study.

Problems or Questions.

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Institutional Review Board (IRB) at:

IRB Chairperson's Name: _____

Address: _____

Telephone: _____

Authorization to Use and Disclose Personal Health Information

The health information that will be obtained from you for use in the study includes the following:

- Information obtained from your medical history, physical exam, or other procedures to determine your eligibility for the study; and
- Information that is created or collected from you during your participation in the study, including the results of various tests and procedures.

By signing this consent, you authorize [STUDY DOCTOR/CLINIC] to use your personal health information to carry out and report the results of this study. [STUDY DOCTOR/CLINIC] will disclose your personal health information to the federal government, who is the sponsor of this study, and to certain organizations working on behalf of the federal government to conduct the study, including 1) The EMMES Corporation located in Rockville, Maryland, who is responsible for collecting and analyzing the data from this study, 2) the Reading Center, located at the Department of Ophthalmology & Visual Sciences at the University of Wisconsin in Madison, Wisconsin, who will receive the photographs of your eyes, 3) the Centers for Disease Control and Prevention in Atlanta, Georgia, who will receive your blood sample should you choose to submit one during the course of the study, and 4) the Nutrition Coordinating Center, located at the University of Minnesota School of Public Health in Minneapolis, Minnesota, who will receive your data from a Food Frequency Questionnaire. This study is also being done at other clinics. The researchers at each site may need to share the personal health information they collect with the researchers from other sites because all of the researchers need to know of any problems called “adverse events” or other issues that happen during the course of the study.

By signing this consent, you also authorize [STUDY DOCTOR/CLINIC] to disclose your health information to regulatory authorities for the purpose of assuring the quality of the study conduct, the quality of data, or for purposes otherwise required by law. Once your personal health information is disclosed to the federal government and its agents or to regulatory authorities, your personal health information may no longer be protected by

federal privacy regulations, and there is a chance that your personal health information will be re-disclosed. Upon disclosure of personal health information, you will be referenced by your study number and not by your name. Your name will not be disclosed without your consent.

In addition, if you consent, off-site employees of The EMMES Corporation will be provided with information on how to contact you. One of these individuals will telephone you up to three months after your next study visit to talk to you about the Cognitive Function study. Like all of your other study data, your Cognitive Function study data will be entered into the computer using your study number only (not your name or any other identifier), and the person who interviews you is bound by the privacy law to not share any of your personal information.

Additionally, **separately from your research data**, The EMMES Corporation will be provided with information on how to contact you.

- At any time during the course of the study you may receive a phone call from a staff member at The EMMES Corporation to check on your condition and to see if you have any questions. You will be called at a time that you indicate is most convenient for you. If you are not available at the time of the call and prefer to call the coordinating center yourself, you will be given a toll-free phone number for that purpose.
- If clinic staff are not able to locate you when we try to schedule your follow-up visits, we will try to contact you through the alternative contact information you have given us.

While the study is in progress, your access to your study records will be temporarily suspended. You will be able to access your information when the study is completed.

It is your free choice to give the Researchers your OK to use and share your personal health information. The term for this OK is called your “authorization.” At any time you

may take back your authorization for the Researchers to use and share your personal health information. The term we use for taking back your authorization is “revoke.” Revoking your authorization means the Researchers may no longer be able to treat you as they do now because you are in the study. But revoking your authorization will not have a bad effect on your current or future health care. Revoking your authorization also does not involve a penalty. And it does not involve the loss of any benefits that you could get otherwise.

You may revoke this consent at any time by sending a written notice to [STUDY DOCTOR/CLINIC] at the following address: [CLINIC ADDRESS]. If you revoke this consent, [STUDY DOCTOR/CLINIC] will stop collecting your personal health information in connection with this study. In addition, [STUDY DOCTOR/CLINIC] will stop using and disclosing your personal health information, except to the extent that [STUDY DOCTOR/CLINIC] has already relied on the information. Personal health information supplied to the federal government and its agents prior to your revocation may still be used by the federal government and its agents.

If you do not sign this consent or if you revoke this consent, you will not be allowed to participate, or to continue participation in the study.

Confidentiality

Information from this study will be submitted to the study sponsor. This information may also be submitted for marketing approval to representatives of government regulatory agencies in other countries where the study drug may be considered. The study sponsor and/or its designee will inspect medical records that identify you. Your study-related records and the consent form you sign may be inspected by the FDA or other regulatory agencies or boards.

All of your study records will be kept confidential to the extent required by law. Your personal identity will not be revealed in any publications or release of results. Most

study-related records would identify you by a number only. However, because of the need to release information to the above-referenced parties, absolute confidentiality cannot be guaranteed.

Your consent for the use and disclosure of your personal health information has no expiration date.

You will receive a signed copy of this form.

Investigator Statement

I discussed this study with this person. He or she was given an opportunity to ask questions and I answered any asked. A signed copy of this consent form is being given to this participant.

Signature of Principal Investigator or Designee

Date

Participant Statement

I agree to participate in this study. I have asked all my questions and gotten answers and have had time to consider this decision.

My signature below also means that I am authorizing the Researchers to use and disclose my personal health information as described in this form. I authorize the release of my medical records to the study sponsor.

By signing this form, I have not waived any of the legal rights that I otherwise would have as a participant in a research study. I have been told that I may ask further questions at any time and that I will receive a copy of this signed consent form for my records.

Name of Participant (printed)

Signature of Participant	Date
--------------------------	------

Signature of Person Obtaining Consent	Date
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Consent Document. Please keep a copy of this document in case you want to read it again.

Second Consent to Participate

The Age-Related Eye Disease Study 2 (AREDS2): A Multi-center, Randomized Trial of Lutein, Zeaxanthin, and Omega-3 Long-Chain Polyunsaturated Fatty Acids (Docosahexaenoic acid [DHA] and Eicosapentaenoic acid [EPA]) in Age-Related Macular Degeneration

Consent to be a Research Subject

Introduction and Purpose

This consent form describes the research study and your role as a participant. In AREDS2 your ophthalmologist will become, in addition, a research investigator and you will become a study participant.

In addition to this consent, there is a booklet that provides information in a different format. Please feel free to take these documents and think about participation. Please read this form carefully. Do not hesitate to ask anything about the information provided. Your doctor or nurse will describe the study and answer your questions. We expect you to be in this phase of the study for up to six years. Approximately [insert number] persons at [Name of Institution] and a total of 4,000 participants in the United States will be enrolled in the study.

It is important that you know the following:

1. Your participation in this study is entirely voluntary, and you may decide to stop or withdraw from this study even after signing this consent.
2. You may choose not to take part in the study and will not lose any benefits to which you are otherwise entitled.
3. You will not receive any monetary compensation for participation.
4. You may receive no benefit from taking part in the study. The study may give us knowledge that will help people in the future.
5. There is no cost to you for participating in this study.

6. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they want to receive. If you have such beliefs, please discuss them with your clinic staff before you agree to take part in the study.
7. There are no monetary costs to you or your insurer for activities performed as a part of this study.
8. In the event you cannot come to the clinic for study visits, you have the option of having an AREDS2 eye doctor and/or AREDS2 coordinator arrange with you to see you at your home. Also, if you move from this area, with your permission the AREDS2 staff will look for another AREDS2 clinic close to your new home so that you can continue your participation in the research study. If there is no AREDS2 clinic near your new home and, if you are willing, we will help you find an eye doctor who will help us complete the rest of your study forms.

Procedures

You will be randomly assigned to one of the four treatment groups: 1) lutein/zeaxanthin tablets and DHA/EPA placebo soft gels; 2) lutein/zeaxanthin placebo tablets and DHA/EPA soft gels; 3) lutein/zeaxanthin tablets and DHA/EPA soft gels; or 4) lutein/zeaxanthin placebo tablets and DHA/EPA placebo soft gels. You will be expected to take one tablet and two soft gels daily for at least five years.

In the original Age-Related Eye Disease Study (AREDS) the AREDS-type supplement was developed. It was found to reduce the risk of progression to advanced AMD. It was studied in people like yourself who are at risk of worsening AMD. You will be asked to participate in a sub-study to determine which parts of the supplement were responsible for any benefit. So in this sub-study we are inviting you to take more supplements. This sub-study is in addition and you do not have to agree to participate.

Participants in this sub-study will take whatever they were assigned to take in the first randomization and will be randomized again to take some or all of the AREDS-type supplement.

The original AREDS-type supplement contains:

- 500 milligrams of vitamin C,
- 400 international units (IU) of vitamin E
- 15 milligrams of beta carotene,
- 80 milligrams of zinc as zinc oxide, and
- 2 milligrams of copper as cupric oxide

You will have a 1 in 4 chance of assignment to any of the 4 groups below.

The AREDS-type supplement is given as a soft-gel capsule to be taken daily. Everyone will take 2 capsules a day.

The groups are:

1	All ingredients
2	All ingredients but no beta-carotene
3	All ingredients but less zinc
4	All ingredients but no beta-carotene and less zinc

Note: If you are a smoker or were in the last year, you can only be placed in groups 2 or 4 which have no beta-carotene.

In addition, if you are currently taking a multivitamin tablet (with or without minerals) and wish to continue taking one, the study will provide it for you. We also ask that you avoid taking other pills containing the study nutrients (lutein, zeaxanthin, DHA, EPA, vitamin C, vitamin E, beta-carotene, and zinc) because it could be harmful and/or effect study outcomes.

In addition to taking the AREDS2 pills, you may be asked to participate in the AREDS2 Nutritional Biochemistry study or the AREDS2 Cognitive Function Study. The main

goals of the Nutritional Biochemistry study are to learn what effect antioxidant supplements may have on blood levels as well as determine what effect they may have on age-related macular degeneration (AMD). Some studies suggest that patients with AMD may have low levels of antioxidants in their bloodstream. Therefore, it is important to continue to follow participants over time and to periodically measure their blood levels and to evaluate its level in reference to progression of AMD.

You may also decide to take part in the AREDS2 Cognitive Function Study.

The purpose of this study is to find out whether the AREDS2 study pills have any possible effect on cognitive function or memory. We will also look for links between memory and eye disease. If you agree, a staff member will call you within the next three months to tell you more about the Cognitive Function Study. After you hear this information, you will decide whether or not you would like to complete the AREDS2 Cognitive Function Telephone Battery. This telephone call will last approximately 20 to 30 minutes, and you may be asked questions about your cognitive function. The Telephone Battery will be tape recorded (audio only) so that the staff can score your answers at a later time. Additional phone calls will occur every other year until the end of the study.

Clinic Visit Procedures

The clinic visit procedures are described in the Participant Information Booklet. We expect that your clinic visits will last approximately 3 to 4 hours.

Nutritional Biochemistry Study (if applicable)

During the randomization visit and selected annual visits (years 1, 3 and 5), select clinics in the Nutritional Biochemistry study will be asked to draw blood from participants to determine blood cholesterol, triglycerides, lutein, zeaxanthin, omega-3 long-chain polyunsaturated fatty acids, vitamin (beta-carotene, C and E), and zinc levels. A clinic staff member will collect 3 tubes of blood from you of about 7 milliliters each (about 4.2

teaspoonfuls total). The blood sample will be sent to the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, for processing and storage. You will not be personally identified outside of [Indicate University affiliation].

Risks

We believe that the risks to participants in the study are small. You should have read about the possible side effects of the study pills and discomfort from photography, dilation, and blood drawing procedures in the Information for Participant Booklet.

Benefits

The study provides you with an opportunity to learn more about your own eyes and eye diseases while you add to medical knowledge that may help others.

Alternatives

There is no alternative treatment for drusen. Persons with large drusen who are at risk for advanced age-related macular degeneration may want to speak with an ophthalmologist about taking the AREDS I supplement – OcuVite PreserVision, which is available as an over-the-counter product in drug stores and many retail chains.

Freedom to Withdraw From the Study

You can stop or withdraw from this study at any time without losing any of the benefits or standard of care treatment to which you may be entitled.

Participant Safety

- Before a study begins, researchers must get approval from their Institutional Review Board (IRB), an advisory group that makes sure a study is designed to protect participant safety.
- During a study visit, doctors will closely watch you to see if you are having any side effects. All the results from your tests and exams are carefully recorded and reviewed. Clinic staff will tell you of any abnormal findings discovered as a result of the study and that may affect your standard of care. It will be up to you to decide whether to follow-up on any findings with your personal doctors.

Participation is Voluntary

Your participation in this research study is voluntary. If you refuse to participate or stop your participation, this will not harm or prejudice your future relationship with your study doctor. Your participation may be stopped by your study doctor or by the study sponsor without your consent. Your study doctor may base such a judgment on events involving yourself or other participants enrolled in the study. We may learn new things during the study that you may need to know. We can also learn things that might make you want to stop participating in the study. If so, you (or your legally appointed representative) will be notified about any new information.

Confidentiality

Your study records (study file) are just like your medical records, which contain confidential and private information. You and your health care team will have access to your records. The Federal Privacy Act protects the confidentiality of your study medical records. However, you should know that the Act allows release of some information from your medical records without your permission; if for example, it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, the sponsor, or other authorized people. The above parties may look at your medical records so that they can see if the data are correct and also determine if federal

regulations are being followed. Your study data are sent to the coordinating center located at The EMMES Corporation in Rockville, Maryland. In that file, you are identified only by a study number and your initials.

Information from this study will be submitted to the study sponsor. This information may also be submitted for marketing approval to representatives of government regulatory agencies in other countries where the study drug may be considered. The study sponsor and/or its designee will inspect medical records that identify you. Your study-related records and the consent form you sign may be inspected by the FDA or other regulatory agencies or boards.

When results of a study are reported in medical journals or at scientific meetings, the people who took part in the study are not named nor identified. In most cases, any information about your research involvement will not be released without your written permission. However, if you sign a release of information form, for example, for an insurance company or private doctor, information from your medical record will be given to your insurance company. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance. All of your study records will be kept confidential to the extent required by law. However, because of the need to release information to the above-referenced parties, absolute confidentiality cannot be guaranteed.

Confidentiality – Blood Drawing Study (if applicable)

The sample of your blood sent to the Centers for Disease Control (CDC) will be identified only by your AREDS2 registration number and initials. No other identifier will accompany the sample, such as name, address, or Social Security number.

Policy Regarding Research-Related Injuries.

If you are injured during this research, you will not automatically be reimbursed for medical care required or receive other payment from the federal government or (this

clinical center). You should notify the Clinical Center Principal Investigator, [PI Name], if you believe any injury has occurred.

Payments

Participants are not paid for taking part in this research study.

Problems or Questions

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Institutional Review Board (IRB) at:

IRB Chairperson's Name: _____

Address: _____

Telephone: _____

Investigator Statement

I discussed this study with this person. He or she was given an opportunity to ask questions and I answered any asked. A signed copy of this consent form is being given to this participant.

Signature of Principal Investigator or Designee

Date

Participant Statement

I agree to participate in this study. I have asked all my questions and gotten answers and have had time to consider this decision.

By signing this form, I have not waived any of the legal rights that I otherwise would have as a participant in a research study. I have been told that I may ask further questions at any time and that I will receive a copy of this signed consent form for my records.

Name of Participant (printed)

Signature of Participant Date

Signature of Person Obtaining Consent Date

I also give my consent to participate in the study evaluating various formulations of the AREDS-type supplements.

- Yes
- No

I also give my consent to participate in the Nutritional Biochemistry study evaluating the effects of the study pills on blood levels and AMD.

- Yes
- No
- Not Applicable – Clinic not in Nutritional Biochemistry study

I also give my consent to receive a telephone call about the Cognitive Function study.

- Yes
- No

Name of Participant (printed)

Signature of Participant

Date

Signature of Person Obtaining Consent

Date

Appendix C. Scheduled Study Evaluation Flow Sheet

	Qualification	Randomization	Telephone	Annual
Read and Sign First Informed Consent	X			
Read and Sign Second Informed Consent		X		
General Assessment				
Inclusion/Exclusion Criteria	X			
Demographics	X			
Run-in dispensing	X			
Study Supplement Dispensing/Accountability		X		X
Adverse Event Assessment			X	X
Ophthalmic Assessment				
Best Corrected visual acuity using E-ETDRS protocol	X ³	X		X
Dilated fundus examination	X	X		X
Fundus Photographs	X			X
Other Assessments				
Family History Questionnaire		X		
Nutritional Biochemistry		X ¹		X ¹
Food Frequency Questionnaire		X		
Cognitive Function Telephone Battery		X ²	X ²	
Cardiovascular Outcome Study Events			X	X

¹ In selected clinics at randomization and annual visits 1, 3 and 5.

² Administered via telephone within three months after randomization and every two years thereafter.

³ Conducting a BCVA is optional at qualification.

Appendix D. Template Authorization for the Release of Medical Records for the Cardiovascular Outcome Study (Should be completed for each Cardiovascular Event)

AUTHORIZATION FOR THE RELEASE OF MEDICAL RECORDS

To: _____
Name of Hospital or Physician

Address: _____

Dear Doctor/Medical Records Clerk:

I am a patient at [NAME OF CLINIC] and am participating in the Age-Related Eye Disease Study (AREDS) II. I authorize you to forward to that study any of the following information requested regarding your treatment of me.

- Discharge summary only, if not available please send the items below:
 - Dates of hospitalization
 - Reason for admission
- History and Physical Examination
- Laboratory test results
- Operative report
- Medications
- Death report (in the future)

