Age-Related Eye Disease Study 2 (AREDS2)
10-Year Follow-On Study, Version 2.0
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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.
<table>
<thead>
<tr>
<th><strong>Study Summary:</strong></th>
<th>Protocol to conduct a final in-clinic visit in selected AREDS2 Clinical Sites as part of the Age-Related Eye Disease Study 2 (AREDS2) 10-Year Follow-On Study</th>
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<tbody>
<tr>
<td><strong>Title:</strong></td>
<td>AREDS2-10YR Follow-On</td>
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<tr>
<td><strong>Sponsor:</strong></td>
<td>National Eye Institute (NEI)</td>
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<td><strong>Study Duration:</strong></td>
<td>One time in-clinic visit</td>
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<tr>
<td><strong>Study Objective:</strong></td>
<td>Provide additional data regarding the incidence of advanced AMD, cataract surgery and lung cancer as well as obtain additional imaging data in the approximately 1,200 AREDS2 study participants enrolled in selected AREDS2 clinical sites</td>
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<tr>
<td><strong>Secondary Endpoints:</strong></td>
<td>Participant reports of incident cardiovascular events; cognitive function battery scores</td>
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<tr>
<td><strong>Number of Study Participants:</strong></td>
<td>Approximately 1,200 AREDS2 participants currently being followed as part of the AREDS2 Follow-on study</td>
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<td><strong>Number of Investigational Sites:</strong></td>
<td>Up to 20</td>
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<tr>
<td><strong>Assessment/Examination Schedule:</strong></td>
<td>One-time in-clinic visit</td>
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## List of Abbreviations and Definition of Terms

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<th>Term</th>
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<tr>
<td>AMD</td>
<td>Age-related macular degeneration</td>
</tr>
<tr>
<td>AREDS2</td>
<td>Age-Related Eye Disease Study 2</td>
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<tr>
<td>BCVA</td>
<td>Best corrected visual acuity</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
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<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
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<tr>
<td>EDC</td>
<td>Electronic data capture</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>ICF</td>
<td>Informed consent form</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>LCPUFAs</td>
<td>Long-Chain Polyunsaturated Fatty Acids</td>
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1. **AREDS2-10YR Follow-On Protocol**

AREDS2 participants completed clinical trial data collection by October 31, 2012 and participants who consented for extended follow-up via telephone are approaching their last year of five (5) years of post AREDS2 clinical trial follow-up as part of AREDS2 Follow-on Study. This protocol describes the procedures to be followed for the collection of additional imaging and data during a one-time, in-clinic visit for approximately 1,200 participants in the AREDS2 Follow-on Study at selected AREDS2 clinical sites. Full details of the AREDS2 clinical trial background, rationale, procedures and information concerning the AREDS2 high dose supplements are available for reference in the AREDS2 Protocol, v 5.2, September 23, 2009. Details of the extended follow-up protocol are available for reference in the AREDS2 Follow-on Protocol, v 1.0, 15 October 2013. Details of the genetics protocol are available for reference in the AREDS2 Genetics Repository Protocol, v 1.0, 12 July 2011.

2. **Study Objectives**

The overall objective of this extended follow-up is to provide data regarding the incidence of late AMD, cataract surgery and lung cancer in 1,200 participants of the approximately 3,200 AREDS2 study participants enrolled in the Follow-on study.

3. **Study Design and Methods**

This is an extension of the multicenter, randomized trial of lutein, zeaxanthin and omega-3 polyunsaturated fatty acids in age related macular degeneration AREDS2 trial. Data for this extension will be collected by staff at selected AREDS2 clinical sites via an in-clinic visit.

4. **Study Conduct**

4.1 **Outcomes**

The incidence of advanced AMD, cataract surgery and lung cancer will be the primary outcomes of the study. Participant reports of incident cardiovascular events will be collected as secondary outcomes.

4.2 **Inclusion Criteria**

To participate in this study, the potential participant **must meet** all of the following criteria:

a. Previously enrolled in the AREDS2 and AREDS2 Follow-on protocols at one of the selected sites for the 10-year follow-up visit.

b. Participant must be offered sufficient opportunity to review and to understand the informed consent form, agree to the form’s contents and provide written informed consent.

4.3 **Exclusion Criteria**

There are no Exclusion Criteria.

4.4 **Study Procedures**

All imaging will be carried out for both eyes.
4.5 Exam Requirements

The following are examinations to be performed at the visit:

a. Informed Consent and Eligibility Criteria Review
b. Targeted Medical/Ophthalmic History
c. Blood draw (from selected participants who did not have blood drawn during AREDS2 participation for DNA)
d. Complete Ophthalmic Examination including:
   1) Manifest refraction
   2) Best Corrected Visual Acuity (BCVA)
   3) Slit lamp biomicroscopy
   4) Dilated fundus examination
e. Ophthalmic Assessments including:
   1) Digital Color Fundus Photographs
   2) Spectral Domain Optical Coherence Tomography (SD-OCT) and OCT Angiography (if OCTA is available)
   3) Wide-field imaging (from selected participants who previously provided wide-field images in AREDS2)

5. Monitoring Participants and Criteria for Withdrawal

5.1 Adverse Experience Reporting

Specific events related to treatment for AMD, occurrence of cataract surgery, diagnosis of lung or other cancers, coronary events including myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, coronary artery bypass and cardiac angioplasty/stent reported by the participant in response to direct questioning, will be recorded as data. The Operations Committee will monitor reported events on a quarterly basis.

The Principal Investigator (PI) is responsible for detecting, documenting and reporting unanticipated problems (UPs), adverse events (AEs), including serious adverse events (SAEs) and deviations in accordance with local IRB requirements and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI.

Serious unanticipated problems, serious adverse events (including deaths) that are not unanticipated problems and serious protocol deviations are to be reported to the IRB as soon as possible and in writing not more than seven days after the PI first learns of the event, unless immediate reporting is waived for specific serious adverse events as noted below. Not serious unanticipated problems and not serious deviations will be reported the IRB as soon as possible and in writing not more than 14 days after the PI first learns of the event.

All adverse events, deviations and unanticipated problems will be summarized and reported at the time of Continuing Review.
5.2 Waiver of reporting

Adverse events that are unrelated to the research will not be reported to the IRB immediately or at the time of continuing review.

5.3 Withdrawal Criteria

Participation in this study is strictly voluntary. Participants may choose to withdraw from this study for any reason at any time without penalty or prohibition from receiving standard medical care.

6. Statistical Considerations

6.1 Primary Outcomes

a. Comparison of the long-term exposure of the randomized AREDS2 treatment (lutein and omega 3 fatty acid main effects and pairwise comparisons of three active arms compared to placebo) on the progression to advanced AMD.

b. Comparison of the long-term exposure of the randomized AREDS2 treatment (lutein and omega 3 fatty acid main effects and pairwise comparisons of three active arms compared to placebo) on incident cataract surgery.

c. Comparison of the long-term exposure of the randomized AREDS2 treatment (lutein main effects) on incident lung cancer.

6.2 Secondary Outcome

Comparison of the long-term exposure of the randomized AREDS2 treatment (omega 3 fatty acid main effect) on the incident participant-reported cardiovascular disease. Similar comparison of long-term exposure of the randomized AREDS2 treatment (omega 3 fatty acid main effect) on changes in cognitive function.

6.2.1 Other Analyses to be Considered a Priority

The following are additional analyses of interest that have been identified as potential outcomes to be considered using the long-term exposure data.

a. Comparison of the long-term exposure of the randomized AREDS2 treatment (lutein and omega 3 fatty acid main effects and pairwise comparisons of three active arms compared to placebo) on the probability of 10 and 15 letter loss in best corrected visual acuity (BCVA).

b. Evaluation of the changes in OPTOS wide-field imaging grading at 10 years and potential genetic associations with peripheral changes of AMD.

c. Incidence of AMD - Neovascular (via telephone capture of data and medical record validation by physician) and GA.

d. Incidence of cataract surgery (via telephone capture of data with medical record validation by physician).

e. Association between cataract surgery and visual outcomes.

f. Assessment of the progression or growth of GA.

g. Evaluation of GA following anti-VEGF therapies.
6.2.2 Blood Draw for DNA

For the approximately 300 participants who did not contribute to the AREDS2 Genetics Ancillary study, we hope to be able to augment our current numbers of participants with DNA for further analyses such as progression of AMD, GA and other secondary outcomes. The DNA will be provided to researchers for research that will benefit public health as determined by the NEI. Researchers who obtain the DNA will have to sign an agreement prior to receiving it that it will only be used for valid research purposes and not for activities that would violate the privacy of the participants.

Phenotypic information as well as fundus images for each specimen will be provided to the AREDS2 Genetic Repository by the AREDS2 Coordinating Center for display in the Repository’s Catalog after sample processing has been completed. This will include basic demographic information such as age, gender, race and ethnicity as well as eye-disease specific information.

6.3 Interim Analyses

No interim analysis is planned.

6.4 Data Quality Assurance

The data will be collected via Electronic Data Capture (EDC) system using eCRFs. The AREDS2 Coordinating Center will have the primary responsibility for assuring that the quality of the data collected and reported in the study are of consistently high quality.

The major quality assurance features of the study are:

a. Standard data collection forms and procedures;

b. Common protocol examination of participants in all participating clinical centers;

c. Central grading of study images;

d. Data entry into the study database and the Clinical Sites;

e. Central, computer driven data editing for missing, invalid and suspect responses; and

f. Regular reporting of performance of all Clinical Sites.

7. Human Participant Protection

All participants will receive a verbal explanation from the Principal Investigator or his/her appropriate designee in terms suited to their comprehension of the purposes, procedures and potential risks of the study. In the opinion of the Principal Investigator or designee, the participants must be capable of comprehending the contents of the informed consent and able to sign an informed consent form, which must be obtained prior to enrollment. The participants will have an opportunity to review the consent form carefully and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves.

The participants’ names will not appear on any of the data forms reported to the Coordinating Center. Participants will be identified by a study number. The information collected will remain confidential.
7.1 Justification for Exclusion of Children

Children will not be eligible for this study, as the condition under study affects primarily adults and no children were enrolled in the AREDS2.

7.2 Qualifications of Investigators

The physicians who will be performing study procedures are experienced in caring for patients with AMD. In addition, they are experienced in conducting studies similar to this protocol. Investigators on this study are clinically credentialed staff and fully qualified to perform study procedures.

The Principal Investigator (PI) has verified that all individuals working on this protocol at his/her site have completed all required training in Human Subject Protections and adherence to the principles of good clinical practices (GCP), or they will do so before assuming any duties for this protocol.

7.3 Refraction and Visual Acuity

Specific certification in electronic ETDRS refraction and visual acuity techniques using the Electronic Visual Acuity (EVA) tester is required for this study. Each person (e.g., physician, optometry professional, ophthalmic technician and/or nurse) who performs these determinations on study participants must be certified. Existing Emmes certifications obtained within the past two years may be grandfathered if candidates are currently certified for similar procedures in other studies and have been actively performing the EVA refraction and visual acuity testing protocol. Visual acuity examiners whose certifications were obtained more than two years ago will need to go through the telephone certification process before performing visual acuity assessments on study participants.

Training and certification in obtaining visual acuity measurements using the EVA tester will be provided prior to study initiation. The Coordinating Center must review and approve any training or certifications not conducted by Emmes staff.

7.4 Photography Certification

Specific certification is required in techniques for color fundus photography and wide-field imaging. Certification will be provided by the central Reading Center for all study staff performing these examinations. The Reading Center may grandfather existing certifications if candidates are currently certified for similar procedures in other studies and have been actively performing the procedures.

8. Study Risks

There are risks associated with the diagnostic procedures required for participants in this study. However, these are all standard procedures that are performed as part of a normal eye and medical exam. 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 an infection, but neither of these problems is very 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 abraded during measurement of intra-ocular pressure or use of a contact lens (used for examination purpose only and not a contact lens used to correct a participant’s refractive error).

Optical Coherence Tomography and OCTA are FDA-approved imaging techniques, which are not associated with any adverse events. Fundus photography and wide-field imaging are not associated with any adverse events, although some participants may experience mild discomfort due to the bright lights.

For participants who have blood drawn, the specimen will usually be taken from the vein in the antecubital space. The only inconvenience would be from the venipuncture itself, which, on occasion, can result in bruising or bleeding. There is a remote risk of fainting or local infection. If any of these conditions arise, they will be treated.

There may be a risk to confidentiality. All precautions will be employed at the clinical sites, Coordinating Center and associated areas such as the Reading Center and the genetics repository. All specimens, images and data entered into the data system will have the participants’ study identification number only; however, the date of birth will be entered into the data system. Samples should be labeled with a unique Specimen ID. The AREDS2 Participant ID will be shown on the shipping manifest but not on the label on the sample tubes. The Specimen ID will be used for display of phenotypic data in the catalog, not AREDS2 Participant ID.

9. Regulatory Requirements

9.1 Informed Consent Form

Before enrolling in the study, each participant must consent to participate after the nature of the scope and possible consequences of the study have been explained in an understandable form. An informed consent form that includes information about the study as required by the IRB will be reviewed and approved by the IRB. Model study-wide consent forms will be provided to assist the clinical sites with their IRB application; however, each clinical site will be able to modify the consent form templates to comply with the requirements of their local IRB or the central IRB. In compliance with HIPAA regulations, consent forms will incorporate language pertaining to the acquisition, use and disclosure of protected health information. Authorization for inclusion of the participant’s study data in public release datasets will be part of the consent. The consent forms for applicable sites will also include language concerning the storage (“banking”) of biological specimens, including DNA, for future analyses and the availability of specimens to investigators and researchers.

Once approved, the participant will be given the document to review and sign. This document will contain all ICH-required elements. The Informed Consent process will be conducted in compliance with ICH GCP guidelines. The Informed Consent form must be in a language understandable to the participant and must specify who informed the participant. For sites whose IRB allow it, a short form written consent and translator may be utilized.

A copy of the signed consent document must be given to the participant or the participant’s legally authorized representative. The Principal Investigator will retain the original signed consent document or follow the policy at their site (e.g., keep only an electronic scanned copy of the signed consent).
The Principal Investigator will not undertake any measures specifically required solely for the study until informed consent has been obtained.

9.2 Communication with the Institutional Review Board

This protocol, the Informed Consent Form, and any information to be given to the participant and relevant supporting information must be submitted to the IRB by the Principal Investigator for review and approval before any study activity is initiated.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB. The Principal Investigator is also responsible for promptly informing the IRB of any protocol changes or amendments and of any unanticipated problems involving risk to human participants or others.

9.3 Study Monitoring Requirements

Monitoring visits are not required as part of this study; however, the Principal Investigator of the study will monitor the study at least annually. The Principal Investigator will also permit Sponsor representatives, US FDA, other regulatory agencies and the Institutional Review Board to inspect facilities and records relevant to this study.

9.4 Electronic Case Report Forms

The primary method of data transmittal to the Coordinating Center will be via a secure, internet-based electronic data capture (EDC) system maintained by the Coordinating Center. The current MOP and access to the EDC system is available to authorized users by the Coordinating Center’s Internet website, where an assigned username and password are required for access. All data transfer 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.

9.5 Disclosure of Data

Participant medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the participant or unless permitted or required by law.

Data generated by this study must be available for inspection upon request by representatives of the US FDA and other regulatory agencies, national and local health authorities, Sponsor representatives and the IRB, if appropriate.

9.6 Data and Sample Sharing Plan

Clinical data will be stored in each site’s secure medical research/hospital record and/or in each site’s secure electronic research databases as well as in the secure electronic databases of the Coordinating Center.

Prior to sharing, data and genetic samples will be stripped of identifiers and may be coded (“de-identified”) or unlinked from an identifying code (“anonymized”). When coded data and genetic samples are shared, the key to the code will not be provided to collaborators, but will remain at NIH.
De-identified data and genetic samples may also be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases. Fundus photographs will be provided to the databases. Although all identifiable data are removed from the images but each image is unique to the individual, there is a small risk that fundus photographs can be used to identify a participant. These databases are not open access; thus, the risk is relatively small. The harm of identifying an individual may be considered small because one can only identify that individual with having a retinal disease. Repositories receiving data and/or genetic samples from this protocol will be restricted access such that investigators obtaining data and/or samples will need to sign an agreement to use the samples for research approved by the NEI and to not violate the privacy of the participants.

Data and genetic samples may be shared with investigators and institutions with a Federal Wide Assurance (FWA) or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

9.7 Retention of Records

When a marketing application is not to be filed as with this Protocol, US FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study, including eCRFs and consent forms, must be retained by the Principal Investigator for two years after the investigation is discontinued and FDA is notified. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor for transfer of any records to another party or moving them to another location.

10. Research Compensation

For this study, there is no monetary compensation for participation. Bausch & Lomb will provide a one-year supply of the AREDS2 vitamin supplements to participants who document consent on their informed consent form that they would like to receive it. This will be an additional year to what they are receiving for participating in the AREDS2 Follow-on telephone interviews. The AREDS2 vitamin and mineral supplements will be sent to the participants directly from Bausch & Lomb.