

MANUAL OF OPERATIONS

CHAPTER 19 – PHASE III

Revised March 25, 2002

19.1 INTRODUCTION

The Age-Related Eye Disease Study (AREDS) is a prospective, natural history study of age-related macular degeneration (AMD) and age-related cataract, two of the four leading causes of blindness in the United States. Study data will be used to calculate rates of progression for both diseases and to identify subgroups of patients at high risk for disease progression. In addition to the natural history study, AREDS includes a randomized clinical trial of high-dose vitamin and mineral supplements (Phase II). Other trials of high dose supplements are listed in Exhibit 19.1.

AREDS enrolled 4,757 participants ages 55 to 80 years between November 1992 and January 1998. By October 2001, the beginning of Phase III, 506 of the enrolled participants are deceased (estimated 5-year mortality rate is 7%) and over 3500 participants are planning to continue in AREDS. AREDS provides a unique resource of persons followed with annual lens and fundus photographs documenting disease status over time. Specific objectives of a five-year extension of follow-up for this cohort are summarized below.

19.2 OBJECTIVES

The AREDS Phase III natural history study provides for at least a five-year extension to the AREDS Phase II clinical trial. The primary objective of AREDS Phase III is to evaluate the clinical course and progression of AMD and cataract for participants previously enrolled in Phase II. Change in visual acuity and disease progression will be collected and assessed. Specific questions that can be addressed include:

19.2.1 Natural History

\$ *Describe age-specific, 10-year progression rates.*

Ten-year rates are appropriate to recognize the chronic nature of AMD and cataract.

\$ *Identify important genetic, ocular, and environmental risk factors for cataract and AMD progression and blindness, with greater precision and confidence.*

AMD and cataract are slowly progressing age-related diseases - many of the participants who are free of either disease at 5 years will develop it by 10 years (i.e., the number of events will at least double). Furthermore, those study participants who remain free of disease into their 80's will become an important cohort to study, especially as controls in genetics studies.

- \$ *Develop disease grading scales as surrogate outcome measures for cataract and AMD by demonstrating association between progression on the grading scales and clinically important outcomes such as blindness, moderate visual acuity loss, need for surgery, and subjective visual function loss as measured by the NEI-VFQ.*

It is important to link progression of severity with functional loss, because future intervention studies may only be possible if we can shorten the length of follow-up needed to detect clinically meaningful treatment differences. To do this we will need more clinically important outcomes than are projected at 5 years. Only eleven percent of persons with good vision at enrollment are expected to have visual acuity of 20/200 or worse (legal blindness) by 5 years and only 1% will be bilaterally blind. For persons enrolling with one blind eye (474), the rate of bilateral blindness is expected to be 20% at 5 years.

19.2.2 Cognitive Function

- *Measure the potential differences in effect of Cognitive Function scores of participants by randomized AREDS Study Medication assignment.*

Associations between dietary intake of antioxidants and zinc and plasma levels with cognitive performance have been examined in a number of epidemiologic studies.¹⁻⁹ AREDS provides an opportunity to study this potential association in the setting of a large randomized clinical trial.

- *Investigate potential associations between cognitive function and AMD and/or cataract development and progression.*

AREDS was designed to improve our understanding of the predisposing factors, clinical course, and prognostic factors of two age-related eye diseases, AMD and cataract. Identification of associations between these eye diseases and cognitive function may further our understanding of the etiology and mechanisms of action of these age-related problems.

19.2.3 Clinical Trial

- \$ *Long term follow-up of study interventions to characterize long term adverse effects and describe the natural history and risk factors for disease progression within the treated cohort.*

The AREDS interventions were pharmacologic doses of antioxidants and zinc. Long term follow-up will be important to characterize ophthalmic and systemic outcomes. Participants will not be restricted to their original treatment assignments during Phase III; however, comparisons will be based on original assignments.

19.3 ELIGIBILITY

- 19.3.1 All participants enrolled in Phase II are eligible to participate in Phase III after signing an Informed Consent Form.
- 19.3.2 Participants initially refusing participation may enroll in Phase III anytime up to one year following Phase III initiation (i.e., by October 2002).

19.4 STUDY OUTCOME VARIABLES

The study outcome variables will be consistent with the variables for Phase II, which include morphologic, visual acuity, and visual function changes. These changes will be assessed annually with photographs and eye exams. Cognitive function will be measured every two years.

19.5 FOLLOW-UP SCHEDULE

All participants who re-consent to participate in Phase III will be followed by clinical examinations annually for at least five more years. Telephone interviews will be conducted at 6-month intervals between examinations to maintain contact and obtain ocular history.

19.6 STATISTICAL CONSIDERATIONS

Unit of analysis. The unit of analysis for the clinical course and prognosis will be either the participant or the eye, depending on the analysis. When paired eyes are included in an analysis the positive correlation between eyes with respect to the variable studied will be considered.

Analytic methods. AREDS is a longitudinal study with multiple outcome variables. When only one time point is being considered, the Student's t-test or its non-parametric analogue, the Wilcoxon-Mann-Whitney test will be used. Multivariate analyses will be used to test specific hypotheses and control for important covariates.

Given the longitudinal design of the study, we will use statistical methods specifically designed for analyzing longitudinal data to account for within subject correlation. (Ref 1) For a continuous outcome variable such as percent change in visual acuity, linear mixed models and the SAS procedure PROC MIXED will be used. Linear mixed models account for within-subject correlations over time using subject-specific random effects.

For categorical or discrete outcome variable specifications we will use general estimating equations (GEEs), which are multivariate analogs of conventional logistic and Poisson regression. GEEs account for correlations among the observations over time obtained from the same subject by constructing a robust covariance matrix in estimation of the standard errors of the regression coefficients.

Exhibit 19.1**Ongoing, Large-scale, Randomized Trial Investigating Antioxidant Vitamins and Their Effect on Age-Related Cataract and AMD**

Trial	Study Population	Agents Tested
Physicians' Health Study II	Approximately 15,000 apparently healthy U.S. male physicians aged 55 years and older	beta-carotene (50 mg on alternate days); vitamin C (500 mg daily); vitamin E (400 IU on alternate days); Multivitamin (daily)
Women's Health Study	39,876 apparently healthy U.S. female health professionals aged 45 years and older	vitamin E (600 IU on alternate days)
Women's Antioxidant Cardiovascular Study	8,171 female health professionals aged 40 years or older who are at high risk for the development of heart disease	beta carotene (50 mg on alternate days); vitamin C (500 mg daily); vitamin E (600 IU on alternate days); and folate (2.5 mg daily), vitamin B ₆ (50 mg daily), and vitamin B ₁₂ (1 mg daily)

Source:

Christen WG, Antioxidant Vitamins and Age-related Eye Disease. Proceedings of the Association of American Physicians 111(1):19, 1999

For analyses of data from both eyes, Cox's proportional hazard model for multivariate time to event data will be used. These methods involve the use of regression coefficients obtained under a working independence assumption and a robust variance estimate for these coefficients that accounts for intra-cluster correlation. The methods will be implemented using either the SAS macro - *phlev* or the SAS macro - *WLW*.

Time-dependent event rates will be computed using the life-table method and the results displayed graphically.

Lost to follow-up. Every effort will be made to encourage participation in the Phase III extension, although as with Phase II 15% are expected to be lost to follow-up or will have died prior to the completion of the study.

Adverse Experiences. Blood level comparisons will be analyzed according to participant original treatment assignment. Some analyses will be stratified by current supplement use. Similar comparisons will be made for cause of hospitalizations over time, both for the original treatment assignment and for current supplementation.

19.7 EXAMINATION SCHEDULE

Informed Consent should be obtained prior to or at the first annual visit for the Phase III natural history study. An overview of the follow-up schedule and sequence of procedures to be performed is provided in Exhibit 19.2.

Participants will be asked to return for a follow up examination annually. A telephone interview will be conducted at non-annual 6-month intervals. Forms to be completed and tests to be performed at each contact are listed below

Non-Annual Telephone Interview

Complete Contact Form
If enrolled in parallel study,
complete Parallel Study Form
Confirm appointment for in-clinic visit
If hospitalized since last visit, complete
Hospitalization form and submit
Discharge Summary.

Annual In-Clinic Visit

Complete In-Clinic Visit Follow-up for or
Missed Visit form
Manifest refraction and Chart 1, 2
Visual Acuity
Take photographs
Eye examination
Obtain IOP
If protocol anomaly, complete Protocol
Anomaly form.
If hospitalized since last visit, complete
Hospitalization form and submit
Discharge Summary.
If enrolled in parallel study, complete
Parallel Study form.
Schedule appointment for next annual
in-clinic visit and non-annual telephone
interview.

19.7.1 Scheduling of Examinations

19.7.1.1 In-clinic Visits and Non-Annual telephone contacts

Forms will be expected for participants with study visit target dates of November 1, 2001 or later. However, every effort should be made to schedule participants who missed visits during the summer of 2001 if they wish to be seen early in Phase III.

A participant should complete one In-clinic visit once per year using the In-clinic Visit form. It is preferred that this visit occurs during the participant's annual (even-numbered) visit windows. However, for those participants who will only be able to come in to the clinic during a nonannual (odd-numbered) visit window, the In-clinic visit may be completed during the participant's nonannual visit window.

Each participant should also complete one Non-Annual telephone contact per year using the Contact form. If the participant is coming in to the clinic during their annual window, the Contact form is completed during the nonannual window. If the participant is only able to come in to the clinic during their nonannual window, the Contact form is completed during the annual window.

19.7.1.2 Special considerations for the first visit of Phase III

As always, attempt to schedule participants according to their next target visit, whether that visit falls in an annual or nonannual window. While this may not always be the case during the first few months of Phase III, the assumptions below are based in part on the expectation that most participants will be scheduled approximately near their target visit.

If the participant's first scheduled visit after October 15, 2001 occurs in an annual window, the participant should be brought in and an In-clinic Visit form should be completed. The exception to this rule is if this participant will only be able to come to the clinic during a nonannual visit window, in which case a Contact form should be completed in place of an In-clinic Visit form at this initial Phase III visit.

If the participant's first scheduled visit after October 15, 2001 occurs in a nonannual window, but the participant or the AREDS investigator wishes to have an In-clinic Visit, an In-clinic Visit form should be completed. A second In-clinic visit should occur during the participant's successive annual visit window, and a second In-clinic Visit form should be completed. Henceforth, only one In-clinic Visit form and one Contact form per year will be expected.

19.7.1.3 Study Visit Windows and Forms Submission

Study visits windows are 3 months prior to target date through 3 months after target date, allowing a 6-month window to conduct study visit. If an In-clinic/home visit or Non-annual telephone contact is not conducted within this specified time frame a missed visit form must be completed and forwarded to the Coordinating Center. Death reports and death certificates should be completed and obtained for participants who have died. Exhibit 19.3 lists all forms and

worksheets required for Phase III and indicates both new forms and Phase II forms revised for Phase III.

19.7.2 Examination Procedures

19.7.2.1 Non-Annual Telephone Interview – Contact Form

The Contact form should be completed after an attempt has been made successfully or unsuccessfully to establish phone contact with the participant in between annual visits. A Parallel Studies form should be complete if the participant has been enrolled in any studies which involve AMD or cataract. Hospitalization forms should be completed for all participants reporting hospitalizations since the last visit. Discharge Summaries should also be obtained and forwarded to the Coordinating Center.

19.7.2.2 Annual In-Clinic Visits – In-clinic Visit Form

Every effort should be made to conduct study visit as close to the target date as possible and before the expiration of the time window. All information described in the above table should be collected at the study visit. If photographs are unable to be taken at an annual visit or retakes are requested, these photographs may be obtained during a scheduled photograph session if convenient. The clinical center staff should use their discretion to determine whether requesting this session will jeopardize that participant's cooperation with the study.

For participants returning to the clinic early in Phase III for an In-clinic visit during a nonannual window (when the participant will otherwise be conducting their In-clinic visits during annual windows), photographs should be taken and labeled with the corresponding visit number only if a visual acuity loss of 10 letters or more is observed for the first time in an eye considered eligible for Phase II.

Blood samples will be taken at the first annual visit for all clinics, to monitor toxicity following the end of the clinical trial and additional blood samples will be collected for the first two annual visits for participating blood-drawing centers. Hospitalization forms should be completed for all participants reporting hospitalizations since the last visit. Discharge Summaries should also be obtained and forwarded to the Coordinating Center.

Exhibit 19.2 PHASE III PARTICIPANT EXAMINATION REQUIREMENTS

Procedure	<u>6-Month study visits</u>	
	Contact	In-Clinic
Initial Informed Consent		
Refraction		x
Visual Acuity		x
Fundus Examination		x
Ocular History	x ¹	x
Medical History		x
Blood Specimen		x ²
Fundus and Lens Photographs		x
Intraocular Pressure		x
Follow-up Interview		x ³
Cognitive Function Questionnaire	x ⁴	x ⁴
Telephone Cognitive Function Questionnaire	x ⁵	x ⁵
Visual Function Questionnaire		x ⁶
Vitamin Usage		x ⁷

¹ Telephone Interview

² Collected at first even-numbered Phase III visit all clinics, Second even-numbered visit only blood drawing clinics

³ Readministered at 5-year, 10-year visit, etc

⁴ Readminister every 2 years (telephone interview at Nonannual/clinic interview during Annual)

⁵ Administer between 6 months and 1-year after first Cognitive Function Questionnaire

⁶ Readministered 5-year, 10-year, etc

⁷ Administer once in 2002 and 2004

Exhibit 19.3 AREDS PHASE III FORM AND REPORT INVENTORY (To be completed by Clinical Centers)

FORMS AND WORKSHEETS

1. Adverse Experience Report (revised)
2. Blood Drawing Questionnaire (revised)
3. Contact Form (new)
4. Death Report (revised)
5. Followup Interview (revised)
6. Genetics Blood Drawing Form *
7. Genetics Specimen Submission *
8. Genetics-Participant Approval of Blood Sample Use
9. Hematocrit Form (new)
10. Hospitalization (revised)
11. In-Clinic Visit Followup (revised)
12. Missed Visit (revised)
13. Parallel Studies Information (revised)
14. Participant Information (revised)
15. Protocol Anomaly (revised)
16. Re-enrollment (new)
17. Supplementation Worksheet (revised)
18. Undispensed Study Medication (revised)
19. Visual Function Questionnaire
20. Vitamin Usage Form (new)
21. Appointment Scheduling*

Cognitive Function Forms

1. Buschke Selective Reminding
2. Center for Epidemiological Studies Depression Scale
3. Cognitive Function Battery - Method of Administration
4. Cognitive Function Refusal
5. Digits Backwards
6. Letter Fluency: A
7. Letter Fluency: F
8. Letter Fluency: S
9. Telephone Interview of Cognitive Status (TICS)
10. TICS Word List Recall
11. Verbal Fluency: Animals
12. Wechsler Memory Scale III - Logical Memory I

UTILITIES

1. Photograph Shipment Tracking System

REPORTS

1. Activity Calendar
2. Laboratory Analyses and Sample Letters (*to be added*)
3. Laboratory Alert Values for Hematocrit and Total Serum Cholesterol Report (*to be added*)

MATERIALS

- | | |
|---|--|
| <ol style="list-style-type: none"> 1. Participant Identification (Card) 2. Reminder for Followup Visit (Card) | <ol style="list-style-type: none"> 3. Reminder for Next Visit (Card) 4. Return Requested Sample Letter |
|---|--|

* System forms only.

REFERENCES

1. Jeandel C, Nicolas MB, Dubois F, Nabet-Belleville F, Penin F, Cuny G. Lipid peroxidation and free radical scavengers in Alzheimer's disease. *Gerontology*. 35: 275-282, 1989.
2. Ortega RM, Requejo AM, Andres P, Lopez-Sobaler AM, Quintas ME, Redondo MR, Navia B, Rivas T. Dietary Intake and Cognitive Function in a Group of Elderly People. *Am J Clin Nutr*. 66:803-809, 1997.
3. Potocnik FCV, van Rensburg SJ, Park C, Taljaard JJF, Emsley RA. Zinc and platelet membrane microviscosity in Alzheimer's disease. *S Afr Med J*. 87: 1116-1119, 1997.
4. Gale CR, Martyn CN, Cooper C. Cognitive Impairment and Mortality in a Cohort of Elderly People. *BMJ*. 312:608-611, 1996.
5. Perrig WJ, Perrig P, Stahelin HB. The Relation between Antioxidants and Memory Performance in the Old and Very Old. *J Am Geriatr Soc*. 45:718-724, 1997.
6. Schmidt R, Hayn M, Reinhart B, Roob G, Schmidt H, Schumacher M, Watzinger N, Launer LJ. Plasma Antioxidants and Cognitive Performance in Middle-Aged and Older Adults: Results of the Austrian Stroke Prevention Study. *J Am Geriatr Soc*. 46:1407-1410, 1998.
7. Zaman Z, Roche S, Fielden P, Frost PG, Niriella DC, Cayley ACD. Plasma Concentrations of Vitamins A and E and Carotenoids in Alzheimer's Disease. *Age and Aging*. 21:91-94, 1992.
8. Morris MC, Beckett LA, Scherr PA, Hebert LE, Bennett DA, Field TS, Evans DA. Vitamin E and Vitamin C Supplement Use and Risk of Incident Alzheimer Disease. *Alzheimer Disease and Assoc Disorders*. 12:121-126, 1998.
9. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ. A Controlled Clinical Trial of Selegiline, Alpha-Tocopherol or Both as Treatment for Alzheimer's Disease. *New Engl J Med*. 336:1216-1222, 1997.