

Chapter 1

BACKGROUND AND RATIONALE

1.1 STUDY OVERVIEW

Eye disorders occurring after age 60 are among the most common causes of visual loss in the United States.¹ With older people making up the fastest growing part of the US population, age-related eye disorders will become even more important in the coming decades. The Age-Related Eye Disease Study (AREDS), which is sponsored by the National Eye Institute (NEI) is a study of factors that may influence the development of two of these disorders, age-related macular degeneration (AMD) and cataract.

Much of what is known about cataract and AMD has stemmed from case-control and prospective studies of select populations from a single community.² Limited natural history or risk factor information is available for either cataract or AMD. For example, our understanding of the role that drusen play in the natural course of AMD is limited, and the importance of nutritional and other risk factors in the development of AMD or cataract is not clear.

AREDS is a multicenter cohort study designed to assess the clinical course, prognosis, and risk factors of both AMD and cataract. Various risk factors for the development and progression of the two diseases will be evaluated. In addition, the effects of pharmacologic doses of (1) antioxidants and zinc on the progression of AMD and of (2) antioxidants on the development and progression of lens opacities will be assessed in randomized clinical trials.

1.2 DISEASE DEVELOPMENT AND COURSE

1.2.1 Age-Related Macular Degeneration

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 persons with 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.

The Macular Photocoagulation Study (MPS), a multicenter, 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.³ But laser photocoagulation is not a cure for the exudative/neovascular form of AMD because many cases are not suitable for treatment and the beneficial effect of treatment appears to

decrease over time. While the exudative/neovascular form of the disease accounts for only 10 percent of all cases of AMD,² 79 percent² to 90 percent⁴ of all cases of legal blindness due to AMD are attributed to the exudative/neovascular form. Substantial central visual loss, including legal blindness, can also occur in the atrophic form of AMD, for which no treatment is available.

AMD is the leading cause of legal blindness in the United States for persons older than 60 years.¹ Patients with AMD tend to lose central vision, which often contributes to a loss of independence as ability to drive and read diminishes. The Framingham Eye Study,² conducted between 1973 and 1975, found that the prevalence of AMD increases with age. As the average life span of our population increases, the incidence and prevalence of blindness from this disease will increase unless successful means of prevention or treatment can be found. Prevalence data from the Framingham Eye Study² and population estimates for the year 2030 obtained from the U.S. Department of Commerce⁵ indicate the number of persons affected with AMD in the United States will grow from 2.4 million in 1970 to 6.3 million in 2030. AMD will thus continue to increase in importance as a public health problem.

1.2.2 Cataract

A cataract is present when the lens loses its normal transparency, resulting in interference with the normal passage of light into the eye. Age-related cataract, often classified into nuclear, cortical, and subcapsular types, is a major public health problem throughout the world and is the third leading cause of blindness in the United States as well as a major cause of visual impairment.⁶ In developing countries, cataracts account for about half of all blindness because resources often are not adequate to provide surgical treatment. Although surgery is an effective treatment for the visual loss caused by cataract, the increasing demand for cataract surgery has placed a growing burden on medical resources. Cataract surgery is now the most frequently performed operation in the United States among persons over age 60, with more than 1 million cataract operations performed annually.

The main sources of data on the prevalence of age-related cataract in the United States are the Framingham Eye Study² and the 1971-72 National Health and Nutrition Examination Survey (NHANES).⁷ Among 2,477 participants in the Framingham Eye Study, age-related lens changes ranging from very mild to severe were present in 42 percent, 73 percent, and 91 percent of persons aged 52-64, 65-74, and 75-85 years, respectively.

Age-related cataract, defined as lens changes that could not be ascribed to specific causes and were accompanied by a visual acuity of 20/30 or worse, was found in 5 percent of persons aged 52-64 years, 18 percent of persons aged 65-74 years, and 46 percent of persons aged 75-85 years. In the 1971-72 NHANES, eye examinations were conducted on about 10,000 persons aged 4-74 years who were part of a probability sample of the US population. Approximately 60 percent of the age group 65-74 years had lens opacities, and 18 percent had lens opacities causing a decrease in vision to 20/25 or worse.

1.3 DISEASE PROGRESSION

In order to describe the morphologic progression of disease it is necessary to have a valid measure of severity of disease. Some systems for classifying and grading the presence and severity of lens opacities have been developed recently, but are still being modified, so that we do not know the rates of progression from specified levels of opacity to cataract requiring surgery. Our understanding of the grading systems for AMD and the significance of morphologic changes associated with AMD is even more incomplete than for cataract. Advanced AMD can have a devastating effect on visual acuity, but little is known about the prognosis of earlier changes associated with AMD, such as drusen and pigment disturbance. It is the aim of AREDS to define which retinal lesions (such as size and extent of drusen or presence and type of RPE abnormalities) are risk factors for progression to visual loss from AMD.

AREDS plans to refine the cataract grading systems and develop an AMD severity scale, as well as evaluate the relationship of both the cataract and AMD classifications to visual acuity and other patient outcomes. This study will provide important information for future studies of these diseases.

1.4 RISK FACTORS

Only limited data are available on the etiology of AMD and age-related cataract. Available evidence suggests that the development of cataract and AMD is a complex process involving medical, environmental, and genetic factors.⁸⁻¹⁰ Demographic factors, medical conditions, medication use, nutritional factors, and ocular as well as other characteristics seem to be associated with increased risk of cataract and AMD. A review of the literature on possible risk factors for cataract and AMD is provided in Chapter 2.

1.5 ANTIOXIDANTS AND ZINC

Recent animal and case-control studies suggest that antioxidants may protect against the development of cataract and AMD, and a small clinical trial has reported that zinc retards the progression of AMD. However, no conclusive evidence of beneficial effects of any micronutrient or mineral has been established (Chapter 2).

1.6 STUDY GOALS

AREDS is a prospective cohort study designed to:

- ! Provide information on the development (incidence), course, and progression of age-related macular abnormalities and lens opacities, including incidence and progression rates.
- ! Evaluate various possible risk factors for development and progression of the two disorders.

The randomized clinical trials will:

- ! Assess the effects of high-dose antioxidants (vitamins C and E and beta-carotene) on AMD and cataract and high-dose zinc on AMD.

Eleven Clinical Centers (Appendix A) will enroll 4,600 participants to meet the study's objectives. The information resulting from AREDS should provide important steppingstones toward preventing these disorders.

1.7 STUDY TIMETABLE

The study period is divided into three phases: Phase I (March 1990 - October 1992), Phase II (November 1992 - September 2001) and Phase III (October 2001 - March 2006). The first 6 months of Phase I (Phase I-A, March 1990 - August 1990) were devoted to planning the study, and the remaining months (Phase I-B, September 1990 - October 1992) were focused on screening and identifying potentially eligible study participants, developing the study protocol, and making other detailed preparations for Phase II. Various advisory groups made recommendations in Phase I regarding the study design and operational details for Phase II.

Participation in Phase I required limited examinations for eligibility and the signing of an informed consent (Phase I Manual of Operations, Appendix B). After eligibility was confirmed, participants were registered and assigned a registration number.

The operational objectives of Phase II were to enroll and randomize at least 4,600 eligible participants in the clinical trials, many of whom will have been identified in Phase I, to follow them for the next 6 to 7 years, and to meet the clinical trial's scientific objectives. The comprehensive Phase II eligibility examinations include measurement of best corrected visual acuity, lens and fundus photographs, and medical history. Phase III will provide additional followup information on this cohort to study the clinical course of and risk factors for cataract and AMD.

Exhibit 1-1 shows the projected timeline for the three phases of the study. For the 10 contract-funded Clinical Centers (Appendix A), the recruitment goal during Phase I was 30 participants per month; for the non-contract-funded NEI Clinical Center, the recruitment goal was 8 participants per month. The complete baseline examination, which establishes participant eligibility for AREDS, is conducted during Phase II. Because not all participants registered during Phase I will be eligible, enrollment will continue in Phase II until each of the 10 centers has enrolled 460 participants or the study has reached the recruitment objectives; the NEI Clinical Center is expected to contribute 100 study participants.

1.8 REFERENCES

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