

Chapter 5

STUDY POLICIES

5.1 ADHERENCE TO MANUAL OF OPERATIONS

The entire AREDS Research Group participates in the development, review, and acceptance of this Manual of Operations. The manual is formally approved by the AREDS Operations Committee, AREDS Executive Committee, and the Data and Safety Monitoring Committee (DSMC). It is essential to the success of the study that all AREDS investigators adhere to the procedures outlined herein. If any AREDS investigators find that, for whatever reason, adherence to these procedures is difficult or not possible, they should discuss the problem with the Study Chairperson or the Protocol Monitor (Section 12.5).

5.2 INFORMED CONSENT

Written consents shall be obtained from each AREDS participant as part of enrollment in Phase I and in Phase II. The Clinical Center must ensure that participants are adequately oriented to the objectives and procedures of AREDS. Prior to enrollment in Phase II participants will be provided with the AREDS Participant Information Booklet to read. Only after the investigator is satisfied that the participant understands the potential risks and benefits of participation in Phase II of AREDS will written consent be obtained.

Informed consent is also needed for any additional research procedures that may be part of an ancillary study and may expose the participant to risk or discomfort.

The signed consent forms are placed in the participant's file at the Clinical Center. The Participant Information Booklet and sample informed consent statements to be used in Phase II are provided in Appendix B.

5.3 PROTECTION OF HUMAN SUBJECTS

Prior to enrolling participants in Phase II each participating Clinical Center, must submit to the Coordinating Center and the NEI Project Office a completed copy of Human Subjects Form No. 596 that has been approved by the local Institutional Review Board (IRB) and copies of the Clinical Centers local IRB approved informed consent statements. In addition, annual IRB approval letters must also be submitted to the Coordinating Center and Project Office. The Coordinating Center will distribute copies of these documents to the Drug Company.

5.4 PUBLICITY

The Operations Committee should be informed of local publicity efforts to enroll study participants. Personnel at each Clinical Center should refer requests from news media for information about AREDS to the center's Clinic Director.

Information given by Clinic Directors should emphasize the following:

- ! AREDS is a collaborative, multi center study.
- ! The local center is only one of many.
- ! The study is funded by the National Eye Institute, National Institutes of Health, Department of Health and Human Services.
- ! Results of the clinical trial will not become available until the end of the trial or meaningful findings emerge, as determined by the Data and Safety Monitoring Committee (Section 4.3.3).

Inquiries for additional information not already in the public domain should be referred to the Study Chairperson.

5.5 DISCLOSURE OF STUDY RESULTS

Because knowledge of interim results of the clinical trial could compromise the efforts by Clinical Centers to enroll and maintain follow up of study participants, reports of such results are submitted by the Coordinating Center only to the Data and Safety Monitoring Committee (DSMC), which is responsible for monitoring the results for safety and efficacy.

The results of the trial will be made available to participating investigators at a time specified by the DSMC and as soon as beneficial or harmful effects clearly are established or the trial has concluded. Investigators should refrain from determining the overall results of the study from their own Clinical Center experience.

Disclosure of AREDS results, at appropriate times, to investigators, participants, the scientific community, and the public will be coordinated closely by the NEI and the AREDS Coordinating Center.

5.6 SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

5.6.1 Generation of Publications and Presentations

The Analysis Planning Committee (Section 4.3.10) will develop procedures for generating scientific publications and presentations emanating from the design and data collection of AREDS

study. These procedures will be reviewed, amended, and approved by the Operations Committee. The Analysis Planning Committee will also invite suggestions for additional papers from AREDS investigators. The Operations Committee serves as the Analysis Planning Committee and appoints writing teams for developing AREDS reports and designates AREDS reports as either Primary or Secondary AREDS reports.

Primary AREDS Reports deal with primary AREDS objectives; Secondary AREDS Reports deal with secondary AREDS objectives or ancillary studies (Section 5.7). Before publication, copies of AREDS Reports are sent to all members of the Executive Committee for information and approval. Reprints of published reports are mailed to each center for distribution to staff and outside consultants. Five reprints of each report are sent to the Coordinating Center for the AREDS library.

5.6.2 Editorial Review

Abstracts of papers to be presented at scientific meetings and manuscripts to be submitted for publication that deal with the design of AREDS or are based on AREDS data, whether they pertain to a single AREDS center, several AREDS centers, or all AREDS centers, must be approved by the Editorial Committee before presentation or publication. Reports on ancillary studies must be similarly approved. The only exception is oral presentations to local groups on the design of AREDS, which do not need to be approved by the Editorial Committee.

Chairpersons of writing teams, in submitting an AREDS report for publication, should include a copy of the approval letter from the Chairperson of the Editorial Committee.

5.6.3 Authorship

Primary AREDS Reports will be numbered serially and authored by the "Age-Related Eye Disease Study Research Group." For example:

Title: Incidence of Progressive Visual Acuity Loss in Advanced AMD.
AREDS Report No. 5.

Author: Age-Related Eye Disease Study Research Group

Secondary AREDS Reports will also be numbered, but they will be authored by the members of the writing team and the AREDS Study Research Group. For example:

Title: Lens Changes in Persons With Advanced AMD. AREDS Report No. 8.

Authors: Jefferson KL, Madison NO, Polk QR and Age-Related Eye Disease Study Research Group

5.6.4 Acknowledgments

Primary AREDS Reports will acknowledge the participation of the AREDS investigators, listed by center, who participated in AREDS for 2 or more years. Membership of major committees will also be acknowledged. Such acknowledgments do not need to be made in Secondary AREDS Reports.

Primary and Secondary AREDS Reports will acknowledge support of the study by contracts from the National Eye Institute, National Institutes of Health.

5.7 ANCILLARY AND PARALLEL STUDIES

Ancillary and parallel studies are investigations that are conducted concurrently with AREDS and involve AREDS participants. These studies must be approved by the AREDS Executive Committee, the Data and Safety Monitoring Committee, and the National Eye Institute. Ancillary studies are AREDS studies: they involve participation by the AREDS Operations Committee and the Coordinating Center or Reading Center. Parallel studies are not AREDS studies: they do not involve participation by the AREDS Operations Committee, the Coordinating Center, or the Reading Center. Ancillary study protocols and summaries are kept in a separate volume available at the Coordinating Center.

5.7.1 Definitions

5.7.1.1 Ancillary studies. An ancillary study meets the following criteria:

- (1) The research is conducted by AREDS investigators on AREDS participants.
- (2) The goals of the study are consistent with AREDS objectives.
- (3) The research requires supplementary clinical observations or procedures on AREDS participants.
- (4) The AREDS Executive Committee, with NEI approval, has designated the study as an AREDS ancillary study, thus endorsing participation by (1) the AREDS Operations Committee and (2) the Coordinating Center or Reading Center in study development, conduct, data processing, and data analysis.

Ancillary studies by individual AREDS investigators or groups of AREDS investigators are encouraged because they can enhance the value of AREDS and increase the motivation and interest of investigators in AREDS. However, to protect the integrity of AREDS and to prevent a drain on AREDS resources, all proposals for ancillary studies, whether or not they involve the need for supplementary funds, must be submitted for approval to the Executive Committee and the DSMC.

5.7.1.2 Parallel studies. A parallel study meets the following criteria:

- (1) The research is conducted on AREDS participants but does not need to be carried out by AREDS investigators or involve AMD or cataract. The research may have started before or after the inception of AREDS.
- (2) The AREDS Executive Committee, with NEI approval, has designated the study as a parallel study, thus precluding the participation in the study by the AREDS Operations Committee and by the Coordinating Center or the Reading Center.

5.7.2 Approval of Ancillary and Parallel Studies

5.7.2.1 Studies conducted by AREDS investigators. An ancillary or parallel study conducted by AREDS investigators must be approved by the AREDS Executive Committee and the DSMC. Approval by the Executive Committee and the DSMC is contingent on local IRB approval. A copy of the local IRB approval must be sent to the Coordinating Center as well as subsequent approvals of modifications. Approval of ancillary and parallel studies by the AREDS Executive Committee and the DSMC is needed to assure that the studies will not:

- ! Adversely affect participant enrollment or cooperation
- ! Jeopardize the public reputation of AREDS
- ! Result in premature release of AREDS outcome data
- ! Complicate the interpretation of AREDS results
- ! Substantially divert study resources at one or more Clinical Centers, the Reading Center, or the Coordinating Center.

Additionally, approval by the Executive Committee and DSMC of ancillary studies, but not of parallel studies, is needed to assure:

- ! the study's scientific merit
- ! the risks to participants do not outweigh potential benefits
- ! the participant's rights are not violated.

Such assurance is not needed for parallel studies because they are not AREDS studies: they do not involve participation by AREDS resource centers. The "approval" given to parallel studies by AREDS is limited to indicating that the studies are not expected to jeopardize the scientific merit of AREDS. Because AREDS plays no investigative role in parallel studies, AREDS has no responsibility for their scientific merit or ethical conduct.

AREDS investigators who wish to conduct an ancillary or parallel study should submit a proposal through the local Clinic Director to the Director of the Coordinating Center, who will distribute it to the Operations Committee. After review of the proposal for completeness and clarity by the Operations Committee, the Director of the Coordinating Center will summarize the committee's comments and forward the proposal and comments for primary review to the Executive Committee, with a copy of the comments to the proponent, and, if approved by the Executive Committee, for secondary review to the DSMC. If appropriate, the Director of the Coordinating Center, before forwarding the materials to the Executive Committee and DSMC, will give the applicant an opportunity to amplify, clarify, or withdraw the proposal. Amended proposals will be reviewed again by the Operations Committee, Executive Committee, and the DSMC. If additional funding is being sought through a peer review mechanism, review by the Executive Committee and DSMC will be requested following notification of a funding award.

Proposals submitted for approval should:

- ! Specify whether the study is intended as an ancillary or parallel study (if the study is approved, the Executive Committee will determine the study's designation).
- ! Briefly describe the objectives, methods, and significance of the study and provide full details on procedures (e.g., examinations, tests, photographs, drawing of blood, additional questionnaires) to be carried out on participants. If intended as an ancillary study, the detail should be sufficient to evaluate the study's scientific merit, as in a National Institutes of Health grant application.
- ! State the numbers of AREDS and non-AREDS participants to be enrolled.
- ! State the amount of time by which AREDS clinic visits will be prolonged.
- ! State the number of non-AREDS clinic visits to be required for AREDS participants and their length of time.
- ! State whether participants will sign an informed consent and, if so, include a copy of the form.

5.7.2.2 Studies not conducted by AREDS investigators. For a parallel study that is not conducted by AREDS investigators, AREDS has no role in approving the study; however, AREDS can play a role in preventing AREDS participants from taking part in parallel studies that are demanding on the participants' time.

As part of the eligibility evaluation to determine availability for examinations at 6-month intervals for at least seven years (Section 3.1.3.3), potential AREDS participants should be asked about their participation in other studies. Persons participating in other studies should not be enrolled in AREDS unless the Clinic Director is assured that this participation will not interfere with their successful participation in AREDS. Although the Clinic Director has no direct control over parallel studies conducted by non-AREDS Investigators, if the Clinic Director becomes aware of a parallel study started after inception of AREDS that may interfere with AREDS, the Clinic Director should appeal to the Investigator of the parallel study to refrain from enrolling AREDS participants.

5.7.2.3 Studies of participants who have advanced AMD. For a study involving AREDS participants who have advanced AMD in each eye, AREDS has no role in approving the study; however, AREDS can play a role in encouraging AREDS participants not to take part in studies that are demanding on the participant's time or may affect the assessment of lens opacity progression.

Studies begun after inception of AREDS are subject to the following guidelines and participation in these studies must be reported to the Coordinating Center on the AREDS Ancillary/Parallel Studies Information form. The general guideline for participation in studies is that such participation should not interfere with participant followup in AREDS and that such participation should not affect the development or assessment of study outcome variables. Special considerations are appropriate for patients who have reached the AREDS study endpoints for AMD.

Such patients may desire to be involved in studies assessing new treatments of end stage AMD.

- ! *Participants with advanced AMD in both eyes:*
Provided such participation does not interfere with continued followup in AREDS, including assessment of lens opacity progression, participants who in each eye have reached end-stage AMD, as defined by AREDS, may be enrolled in parallel studies of AMD.
- ! *Participants with advanced AMD in one eye:*
Provided such participation does not interfere with continued followup in AREDS, including assessment of lens opacity progression, participants who have, in one eye, reached end-stage AMD, as defined by AREDS, may be enrolled in studies of AMD that require non-systemic treatment in the eye with advanced AMD only.
- ! *Participants without advanced AMD in either eye:*
Unless the study has been approved by the AREDS Executive Committee and DSMC, participants who have not reached end-stage AMD as defined by AREDS in either eye, may not be enrolled in studies of AMD. Participants with a natural lens remaining may not be enrolled in parallel studies of cataract using systemic medications, or studies of drugs with cataractogenic potential.
- ! *All participants:*
When the primary interest of parallel studies and the treatment plan does not relate to AMD or cataract or interfere with the assessment of AMD or cataract, whether their nature is ophthalmic or not, AREDS participants may be enrolled in them. Examples are studies involving prostate cancer, sleep disorders, cirrhosis, psoriasis, dry eye, etc. Efforts should be made to prevent participation in these studies from interfering with continued followup in AREDS. Clinical Center staff will report such participation to the Coordinating Center on the AREDS Ancillary/Parallel Studies information form.

5.7.2.4 Review and approval of genetic ancillary studies. AREDS or non-AREDS investigators who wish to conduct a genetics ancillary study should submit a proposal to the Director of the Coordinating Center, who will distribute it to the Operations Committee. After review of the proposal for completeness and clarity by the Operations Committee, the Director of the Coordinating Center will forward the proposal to the Coordinating Center's genetics consultant for review of methodology and scientific merit. Following review by both the Operations Committee and genetics

consultant the Coordinating Center Director will summarize the reviewers' comments and forward the proposal and comments for primary review to the Executive Committee, with a copy of the comments to the proponent, and, if approved by the Executive Committee, for secondary review to the DSMC. If appropriate, the Director of the Coordinating Center, before forwarding the materials to the Executive Committee and DSMC, will give the applicant an opportunity to amplify, clarify, or withdraw the proposal. Amended proposals will be reviewed again by the Operations Committee, genetics consultant, Executive Committee, and the DSMC. If additional funding is being sought through a peer review mechanism, review by the Executive Committee and DSMC will be requested following notification of a funding award.

Proposals submitted for approval should:

- ! Describe the objectives, methods, and significance of the study and provide full details on materials required and procedures (e.g., quantity of DNA, methods of DNA analyses, laboratory quality control procedures). The detail should be sufficient to evaluate the study's scientific merit, as in a National Institutes of Health grant application.
- ! State the numbers of AREDS and non-AREDS participants to be included with a statistical justification for the sample size.

5.7.3 Funding and Publication of Ancillary and Parallel Studies

5.7.3.1 Funding. NEI AREDS contract funds may not be used to support the conduct of ancillary or parallel studies. For additional funds, the investigator may wish to submit an National Institutes of Health R01 grant application or to apply to another funding agency. If no additional funds are required, the investigator may proceed with the study as soon as it is approved by the Executive Committee and DSMC.

5.7.3.2 Publication.

Abstracts and manuscripts authored by AREDS investigators. Abstracts and manuscripts of ancillary or parallel studies that are authored by AREDS investigators and are intended to be presented at scientific meetings or submitted for scientific publication must be reviewed and approved by the AREDS Editorial Committee (Section 4.3.10). The AREDS Executive Committee will review these abstracts and manuscripts to assure that they do not compromise the conduct of AREDS or the interpretation of AREDS results.

For parallel studies, the review will also assure that the documents avoid mentioning AREDS. The NEI may grant an exemption from full review.

Abstracts and manuscripts of parallel studies not authored by AREDS investigators. Because these abstracts and manuscripts are beyond the direct control of AREDS, there is no official review role for AREDS. Nevertheless, AREDS investigators should request their colleagues who are conducting these studies to avoid referring to AREDS in their publications and presentations.

5.8 ADVERSE EXPERIENCE REPORTING

Bausch & Lomb Pharmaceuticals, as a sponsor of an Investigational New Drug application (IND), must report to the Food and Drug Administration (FDA) any adverse experiences associated with the AREDS study medication. A description of Clinical Centers' requirements for reporting adverse experience is provided in Chapter 7. The Coordinating Center's reporting requirements to the DSMC and Bausch & Lomb, and Bausch & Lomb's reporting requirements to FDA are provided in Chapter 11.

5.8.1 Definition of the Adverse Experience

An adverse experience is defined as any toxicity, reaction, event or effect which may possibly be associated with the use of the AREDS study medication. As little is known about potential adverse experiences related to high dose vitamin and mineral supplements, expected reactions associated with the supplement may be difficult to specify in advance.

5.8.2 Adverse Experience Reporting and Management

FDA regulations set out conditions, responsibilities, and requirements related to the sponsorship of clinical trials for investigational drugs. These regulations mandate such responsibilities as monitoring for adherence with good clinical practice and record keeping; and documenting of supplement accountability and reporting of adverse experiences.

In AREDS, the identification and assessment of an adverse experience related to a study intervention presents special problems for the investigator and drug company (IND sponsor) because many participants are likely to develop symptoms unrelated to the study intervention. Often this assessment cannot be made at the time of the adverse experience and requires a retrospective review of study data. The centralization of information on adverse experience makes possible a more accurate determination of the degree to which an adverse event was, in fact, study medication-related.

The AREDS Adverse Experience Reporting (AER) system has been developed to ensure timely and accurate reporting of adverse experiences to comply with FDA regulations, to assess study risks, and, if necessary, disseminate information to the investigators and/or modify the study protocol. The AREDS AER system meets regulatory requirements and provides for evaluation of adverse experiences in the context of a multi center clinical trial allowing for comparison of adverse experiences by intervention type. The adverse experience data will be used to prepare routine regulatory reports, study analyses, and other special reports.