

## **Chapter 4**

### **STUDY ORGANIZATION**

#### **4.1 INTRODUCTION**

The participating investigators and centers in AREDS collaborate through an organization designed to maintain a continuity of operations and to facilitate effective communication and cooperation among the units. Exhibit 4-1 outlines the organizational structure of AREDS. In addition to a Study Chairperson, there are directors for the lens and retina projects of the study. These three individuals and representatives from the Coordinating Center, Reading Center, and the NEI comprise the Operations Committee, which is responsible for day-to-day operations. All major decisions are reviewed by the AREDS Executive Committee, which consists of all Clinic Directors and representatives from the Coordinating Center, the Reading Center, the Coordinators' Group, and the NEI. Major decisions are reviewed by the Data and Safety Monitoring Committee and the NEI Project Team.

#### **4.2 PARTICIPATING UNITS**

The success of a multicenter endeavor depends on the cooperation of the staff in all centers to perform their tasks and responsibilities in an efficient, effective, and timely manner. The participating centers are shown in Exhibit 4-2.

##### **4.2.1 Clinical Centers**

Clinical Centers are responsible for recruiting and examining study participants. Each Clinical Center is supported by a separate contract with the NEI. Key center staff are the Clinic Director, Clinic Coordinator, and Clinic Monitor.

The Clinic Director (an ophthalmologist) supervises the Clinical Center and represents the center at meetings of the Technical Group. The Clinic Coordinator is responsible for critical matters such as:

- ! Scheduling appointments
- ! Ensuring the accuracy, completeness, and consistency of data reported
- ! Submitting fundus and lens photographs to the Reading Center

- ! Handling communications on data processing matters concerning study forms, edit messages, and ocular photographs, as appropriate with the Coordinating Center and Reading Center
- ! Maintaining the participants' interest in the study and encouraging each participant to comply with the study medication.

The Clinic Monitor ensures adherence with the AREDS Manual of Operations and participates in regularly scheduled, structured telephone calls with the Protocol Monitor from the Coordinating Center (Section 12.4.2).

The staff of the Clinical Center carry out the provisions of the Manual of Operations. They are responsible for registering and maintaining follow up of all participants from their clinic. The responsibilities of the Clinic Director, Clinic Coordinator, and Clinic Monitor are further defined in Chapter 13.

#### 4.2.2 Coordinating Center

The Coordinating Center, located at The EMMES Corporation, Potomac, Maryland, is responsible for developing the Manual of Operations, collecting and analyzing study data, ensuring that the provisions of the Manual of Operations are carried out by all participating units, and coordinating study activities. Coordinating Center staff include professionals in biostatistics, epidemiology, data processing, administration, and communication coordination. Consultants are used to supplement the staff for appropriate specialized tasks.

Coordinating Center staff have major responsibility for developing the statistical design, establishing the operational and analytical methodology, and analyzing the data. Coordinating Center staff are also responsible for collecting, editing, analyzing, and storing all data received from the Clinical Centers, the Reading Center, and the Central Laboratory. Some of the specific functions of the Coordinating Center staff are to:

- ! Collaborate with other study investigators in developing study procedures, forms, and the Manual of Operations
- ! Coordinate communications among the centers
- ! Coordinate certification of clinic staff and the Clinical Centers
- ! Assist in training clinic staff in the study procedures
- ! Review all data transmitted on standardized AREDS forms for completeness and accuracy
- ! Create computerized data files for AREDS data
- ! Prepare periodic reports on the performance of the Clinical Centers

- ! Analyze periodically the frequency of specified events and report to the Data and Safety Monitoring Committee
- ! Prepare recruitment, technical, and statistical reports for meetings
- ! Assist in preparing scientific reports for publication.

Detailed Coordinating Center procedures are presented in Chapter 14. Additional details are included in the Coordinating Center Procedures Manuals, which are maintained at the Coordinating Center.

#### 4.2.3 Reading Center

The Reading Center, located at the University of Wisconsin, Madison, Wisconsin, is responsible for making the necessary modifications in the Neitz and slit lamp cameras for all clinics, training photographers in the use of these cameras, certifying fundus and lens photographers, assessing the quality of lens and fundus photographs, and grading the lens photographs for opacities and the fundus photographs for macular abnormalities. The results of photographic evaluations will be forwarded to the Coordinating Center for collation with other data.

The Reading Center is responsible for storing photographs obtained during the study. The procedures to be used are described in Chapter 15. During Phase I, staff will store and evaluate photographs on only a sample of eyes; during Phase II, staff responsibilities will be expanded to include evaluation and storage of lens and fundus photographs of all participants.

#### 4.2.4 National Eye Institute (NEI)

The NEI, the funding agency for AREDS, is responsible for all scientific aspects of the study. The Institute is accountable to higher levels of the Executive Branch, the Congress, and the public for the use of Institute funds and is ultimately responsible for the conduct of the study. The Institute's Director makes final decisions on recommended protocol changes and on other issues of importance to the overall conduct of AREDS.

Representatives of the NEI participate in all scientific activities of AREDS and are responsible for administrative matters related to funding of the centers.

#### 4.2.5 National Institutes of Health, Research Contracts

The responsibility of negotiating budgets with the units participating in AREDS and their business offices lies with the Office of the Director, Office of Administration, Office of Contracts Management, Division of Research Contracts, Contracting Officer.

#### 4.2.6 Drug Company

AREDS is supported in part by Bausch & Lomb Pharmaceuticals (originally Storz Ophthalmic Pharmaceuticals, subsequently owned by Bausch & Lomb). Bausch & Lomb will provide AREDS with adequate supplies of Centrum<sup>®</sup>, placebo, and study tablets to conduct Phase II of AREDS and will hold the Investigational New Drug Application (IND) for the study medications. In addition Bausch & Lomb will support in part the conduct of the clinical trial. A representative from Bausch & Lomb will serve as a nonvoting member of the Data and Safety Monitoring Committee.

#### 4.2.7 Drug Distribution Center

The United States Public Health Service (USPH) Supply Service Center located in Perry Point, Maryland will receive study supplements and placebo from Bausch & Lomb and will be responsible for packaging and distributing the supplements to the Clinical Centers.

#### 4.2.8 Central Laboratory

The Centers for Disease Control (CDC) in Atlanta, Georgia will serve as the Central Laboratory for AREDS. The Central Laboratory is responsible for (1) training participating Clinical Center personnel in procedures for blood sample collection, processing, and shipping and (2) the receipt and analysis of blood samples. The results of the analyses will be forwarded to the Coordinating Center for collation with other data.

#### 4.2.9 Nutrition Coordinating Center

The University of Minnesota, under contract with the AREDS Coordinating Center, serves as the Nutrition Coordinating Center (NCC) for AREDS. The NCC will produce nutrient values corresponding to the responses on the Food Frequency Questionnaire completed by AREDS participants. In addition, staff at the NCC will conduct approximately 400 24-hour dietary recall interviews with 200 randomly selected AREDS participants.

### **4.3 STUDY ADMINISTRATION**

#### 4.3.1 Study Chairperson

The NEI Director appoints the Study Chairperson, who is primarily responsible for the scientific direction and administration of AREDS. The Study Chairperson:

- ! Advises the NEI Director on data monitoring and other issues of importance to the overall conduct of the study
- ! Develops and maintains, with advice from other study participants, an organizational structure that meets the needs of the study and the NEI

- ! Remains informed of all operational aspects of the study and, working within the organization developed, formulates policy and takes necessary action to ensure the smooth operation of the study
- ! Appoints study participants and nonparticipants to appropriate positions and committees
- ! Serves as Chairperson of the AREDS Executive Committee and Operations Committee and is a nonvoting member of the Data and Safety Monitoring Committee.

The Study Chairperson is appointed for the duration of the study. If the Study Chairperson is unable to serve because of resignation, death, or serious illness, the NEI Director will appoint a new chairperson. If the Study Chairperson is ill or unable to fulfill his or her obligation for a limited period (up to 6 months), he or she, in conjunction with the NEI Director, may appoint an Acting Chairperson for that period.

#### 4.3.2 NEI Project Team

The NEI Project Team consists of NEI staff from the Division of Biometry and Epidemiology, the Office of Health Education and Communication, and the Vision Research Program Collaborative Clinical Research of the Division of Extramural Research. The Project Team monitors the study and advises the NEI Director on decisions relating to the conduct of the study.

The AREDS Project Officer designated by NEI has overall responsibility for representing the NEI and is an ex-officio member of the Executive Committee; an ex-officio, nonvoting member of the Data and Safety Monitoring Committee; and a voting member of the Operations Committee.

The NEI Office of Health Education and Communication handles all publicity for AREDS. Press inquiries about the study are referred to this office.

#### 4.3.3 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) is responsible for:

- ! Reviewing the study design and, as appropriate, recommending design changes
- ! Assessing study data, particularly for adverse and/or beneficial effects of treatment
- ! Minimizing risks to participants
- ! Recommending changes in the study protocol as may be warranted from a review of the study data

- ! Reviewing for approval ancillary and parallel studies proposed by AREDS investigators (Section 5.7)

The Study Chairperson communicates the results of DSMC deliberations and recommendations and his or her own opinion to the NEI Director, who has ultimate authority in these matters. The NEI Director reviews the recommendations and, after obtaining additional advice as needed, communicates his decisions to the Study Chairperson and the AREDS Executive Committee.

DSMC members, who are senior scientists, are appointed by the Study Chairperson with the approval of the NEI Director (DSMC members are listed in Appendix A). The Chairperson of the DSMC is designated by the NEI Director. The voting and nonvoting members are:

Voting members

- ! Two ophthalmologists
- ! Two statisticians or epidemiologists
- ! One bioethicist
- ! One nutritional epidemiologist
- ! Other members, as appropriate.

Nonvoting members

- ! Study Chairperson
- ! AREDS Project Officer
- ! Other NEI staff
- ! Co-directors of the Coordinating Center
- ! A Co-director of the Reading Center
- ! Bausch & Lomb Pharmaceuticals representative
- ! FDA representative.

In reviewing the study data, the DSMC will recommend appropriate analyses to answer the questions posed in the study design. After review of each report, the DSMC will make specific recommendations on whether to continue the study with or without protocol change, or to stop any aspect of the study. Recommendations may include majority and minority opinions.

The DSMC reviews data monitoring reports at 6-month intervals or more frequently if warranted. It meets annually, or more often if needed. Any DSMC member may request an additional meeting to discuss the results of interim DSMC reports. Individual votes are recorded at meetings.

Committee members are expected to:

- ! Acquire a detailed knowledge of the AREDS study design and goals.
- ! Attend annual meetings of the DSMC, which are generally held in Bethesda, Maryland. One or two additional meetings per year may be scheduled during particularly active periods of decision making.

- ! Devote 4 to 5 hours to prepare for each meeting by studying DSMC reports and other material submitted by the Coordinating Center and other study units.
- ! Review interim DSMC reports and respond to questionnaires on the need for a meeting or conference call of DSMC members.
- ! Suggest analyses, as appropriate, to be included in DSMC reports prepared by the Coordinating Center.

#### 4.3.4 Executive Committee

The AREDS Executive Committee assists the Study Chairperson in the scientific administration of the study. The Executive Committee discusses and helps formulate and implement all policy decisions related to the conduct of AREDS.

The Executive Committee consists of:

- ! The Operations Committee (which consists of the Study Chairperson, Directors of the Lens and Retina Projects, AREDS Project Officer, Director of the NEI Clinical Center, and Director of the Coordinating Center and a Co-Director of the Reading Center)
- ! All Clinic Directors
- ! Chairpersons of the technical committees
- ! Chairperson of the Coordinators' Group (which consists of all the Clinic Coordinators, the Database Administrator and Protocol Monitor from the Coordinating Center, and the Coordinator from the Reading Center).

The following observers attend Executive Committee meetings:

- ! NEI Project Office staff
- ! Chairperson-elect of the Coordinators' Group who is elected to succeed the current chairperson.

The Study Chairperson, at his or her discretion, may appoint additional voting and nonvoting members for 1-year renewable terms.

The functions of the Executive Committee include:

- ! Recommending to the NEI Director changes or modifications in the AREDS protocol that may be necessary or desirable (but not based on DSMC reports).
- ! Ratifying major changes in the Manual of Operations.

- ! Reviewing and approving all ancillary studies.
- ! Advising and assisting the Coordinating Center, Operations Committee, and technical committees on operational matters.
- ! Resolving operational problems brought to the Executive Committee by investigators, coordinators, the Coordinating Center, the Operations Committee, or the Reading Center.
- ! Monitoring the performance of all participating centers based on information provided by the Coordinating Center and Operations Committee. This evaluation includes assessment of the quality of data collected by center staff and adherence to the protocol. The Executive Committee advises the NEI on the performance of participating centers and may recommend that NEI invite new participants or terminate centers showing unsatisfactory performance.
- ! Reviewing decisions and recommendations of the Editorial Committee (Section 4.3.10).
- ! Assuming other responsibilities at the request of the Study Chairperson or the NEI Director.

The Executive Committee meets annually during the Technical Group meeting. Additional meetings of the Executive Committee may be called by the Study Chairperson.

#### 4.3.5 Operations Committee

The Operations Committee is the operational arm of the AREDS Executive Committee. The committee:

- ! Reviews chapters of the Manual of Operations, study forms, minutes, newsletters, and other materials
- ! Assists the participating units in the performance of their duties
- ! Monitors the performance of these units in accordance with the AREDS protocol
- ! Evaluates the efficiency and ability of the units to meet the needs of the study as defined by the protocol, the Study Chairperson, the Executive Committee, and the NEI.

The members of the committee are:

- ! The Study Chairperson
- ! Directors of the Lens and Retina Projects
- ! AREDS Project Officer
- ! Director, NEI Clinical Center

- ! Co-directors, Coordinating Center
- ! A Co-director, Reading Center.

The Operations Committee reviews the activities of all study units either by direct contact or from reports of groups responsible for monitoring specific aspects of study activities. Members of the Operations Committee meet or confer on the phone frequently, and usually at least once a month.

If the performance of a study unit is unsatisfactory, the Operations Committee acts to remedy the situation. If no improvement in performance is noted, the committee may recommend that the Executive Committee consider further action.

#### 4.3.6 Technical Group

The Technical Group is composed of all study personnel, and its meetings are a forum for disseminating information and discussing problems. Face-to-face discussion of study activities and the opportunity to interact personally contribute to the development of rapport among team members and encourage smooth operation in such a large multicenter clinical study. The units of the Technical Group are the Clinic Directors, the Coordinators' Group, and the technical committees.

The Technical Group meets at least annually. The Clinic Director (or a professional representative) and the Coordinator from each center attend all meetings. Each center must be represented. Technical Group meetings are open meetings and all members of the study are invited; however, funding is provided only for the Clinic Directors and Coordinators. Other personnel from each center, including physicians, photographers, coordinators, nurse-clinicians, secretaries, and paramedical personnel may be invited to participate, with funding, in special training sessions or special meetings, at the discretion of each Clinic Director and as approved by NEI. The Technical Group reviews all decisions of the Executive Committee concerning clinic procedures. Policy dictated by NEI requirements or data monitoring results does not require approval by the Technical Group. Representatives from each center and the NEI Project Office can cast two votes at each meeting.

#### 4.3.7 Coordinators' Group

The voting members of this group are the Coordinators from each Clinical Center; the nonvoting members are the Coordinator from the Reading Center and the Database Administrator and Protocol Monitor from the Coordinating Center, as well as other study coordinators that may be attending the meeting. The group, which meets at least annually in conjunction with meetings of the Technical Group, is responsible for providing information to the Study Chairperson about the logistical aspects of the study protocol and procedures as they relate to each Clinical Center. The Chairperson of the Coordinators' Group, a Clinic Coordinator elected by the Clinic Coordinators, is responsible for preparing the agenda for the meeting, based on comments and suggestions solicited from the group. The Operations Committee reviews and comments on the draft agenda and, after the meeting, on any recommendations from the Coordinators. The Chairperson is also a voting member of the AREDS Executive Committee.

Elections for Chairperson are conducted annually during the Coordinators' Group meeting, with each Clinical Center having one vote. The person elected serves a one-year term as Chairperson beginning January 1st of the following year.

#### 4.3.8 Training and Certification Committee

A Training and Certification Committee, appointed by the Study Chairperson, will develop a training program and establish certification criteria (Chapter 9).

#### 4.3.9 Technical Committees

Other study committees may be formed as needed, with committee chairpersons appointed by the Study Chairperson.

4.3.9.1 Mortality and Morbidity Committee. This committee is responsible for reviewing medical records and making final classifications of all cardiovascular and other medical endpoints. All deaths reported during Phase II of AREDS will be reviewed and coded by the Mortality and Morbidity Committee. Mortality findings will be used to evaluate the effect of pharmacologic doses of the nutrients used in the study on mortality among the AREDS participants.

In addition to classifying mortality, the Mortality and Morbidity Committee will classify all hospitalizations reported by AREDS participants.

4.3.9.2 Other committees. (to be defined)

#### 4.3.10 Editorial Committee

The Editorial Committee, appointed by the Study Chairperson, is responsible for formulating and implementing AREDS editorial policy. The Clinic Directors and Clinic Coordinators serve as the Editorial Committee with the Study Chairman as the Chair of this committee. All AREDS manuscripts for publication and presentation must be approved by the Editorial Committee. Manuscripts on treatment effect on primary endpoints must also be approved by the DSMC and the NEI Director.

#### 4.3.11 Analysis Planning Committee

The Analysis Planning Committee members are appointed by the Study Chairperson. The Operations Committee serves as the Analysis Planning Committee. The functions of the Analysis Planning Committee include the following:

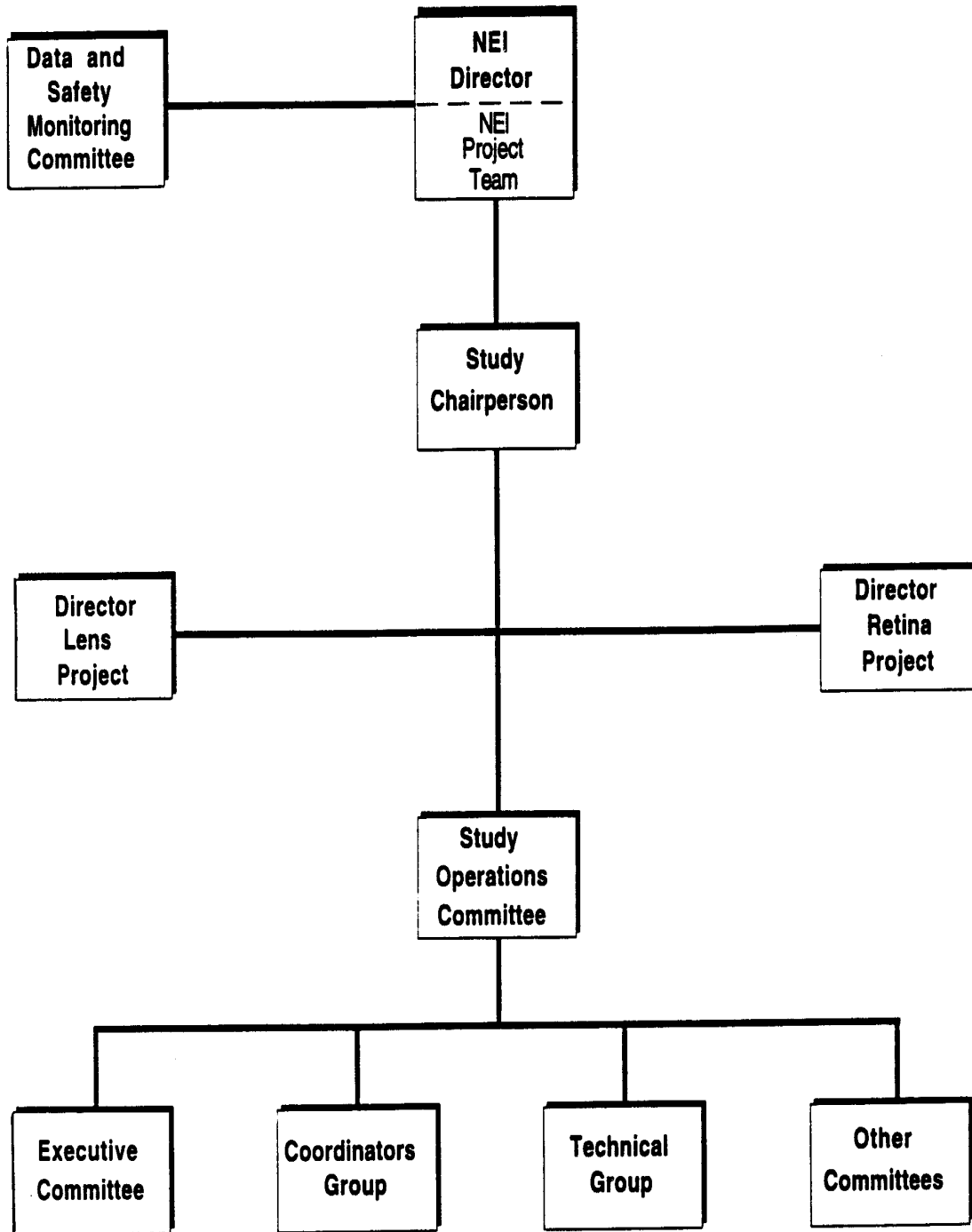
- ! Make specific proposals or review submitted proposals for analysis of AREDS data
- ! Set priorities for scheduling work on these analyses

- ! Appoint writing teams to prepare manuscripts describing the results of these analyses
  
- ! Designate AREDS reports as either Primary or Secondary (Section 5.6).

The Analysis Planning Committee reviews proposals for the analysis of data and preparation of manuscripts. Proposals must include a background and brief review of the literature, a clear statement of the research hypothesis, the specific data items to be used in the analyses, and a description of the proposed data analyses. The literature review should summarize relevant material but not be as detailed as the review that will appear in the manuscript. The major research questions to be answered should be identified clearly and succinctly. Table shells and suggested specific analyses also should be included.

Proposals will be reviewed by mail by at least two members of the Analysis Planning Committee, who will assign tentative priority scores. The proposals will then be reviewed by the full committee at a scheduled meeting, during which the committee will assign a priority ranking to each proposal. Analyses will be performed using available personnel and funds in the rank order assigned by the Analysis Planning Committee.

Exhibit 4-1. AREDS ORGANIZATIONAL CHART



**Exhibit 4-2. AREDS PARTICIPATING UNITS**