

Chapter 11

DATA ANALYSIS AND REPORTING

The AREDS analysis plan will be designed to carefully monitor participant accrual, data quality and timeliness, participant eligibility rates, adverse reactions, visual function parameters, and other outcomes. While detailed analyses of individual studies will be performed periodically, the overall progress of the study will be monitored continuously. Technical and administrative reporting requirements for AREDS consist of both interim and final reports on the scientific efforts. A complete discussion of the outcome variables and the sample size and statistical considerations is provided in Chapter 3.

11.1 ANALYSIS PLAN

The analysis plan for AREDS will be developed by the statisticians and epidemiologists at the Coordinating Center, in collaboration with the Data and Safety Monitoring Committee (DSMC) and the Analysis Planning Committee. An initial plan will be designed during Phase I and subsequent modifications will be made as the study matures. Key aspects of the plan will include monitoring of data quality, study progress, safety, and efficacy. Analyses will be scheduled to coincide with the annual planned meetings of the DSMC and the planned meetings of the technical group. Database assessments will be performed monthly by the Coordinating Center to evaluate the quality of the database. In addition to these planned analyses, the Coordinating Center will expect to conduct various unplanned analyses precipitated by evolving project needs. Requests for such analyses will likely come from the DSMC and the Operations Committee, and may be suggested by the statisticians at the Coordinating Center.

11.1.1 Specification of Analysis Database

Prior to performing a scheduled analysis, the master file will be copied into an analysis file. This analysis file is date-stamped with a closure date to indicate the last day for which data were included. The master file will continue to incorporate new data from the Clinical Centers, while the analysis file is frozen. The closure date provides a reference with regard to the currency of the data on which the analyses are based. Typically, the choice of a date to close the file for analysis depends on the type and quantity of the analyses to be performed. Files will likely be closed 2 to 3 months prior to a scheduled meeting.

11.1.2 Reports for Publication

The Coordinating Center will work with the Analysis Planning Committee in preparing a proposed schedule of analyses for disseminating information resulting from AREDS to the scientific

community. This schedule will be based on the maturity of the data and the study. Presentations on study methods and baseline data will be scheduled during and after the conclusion of the recruitment phase. The timing of the release of reports on outcome data will be based on the recommendation of the DSMC.

11.2 EXPECTED ASSESSMENTS OF THE DATABASE FOR QUALITY CONTROL

Assessments of the database will occur as scheduled in the analysis plan. These assessments will be targeted at maintaining the database integrity, monitoring clinic adherence to the protocol, and assessing cumulative baseline variables (e.g., participant characteristics), outcome variables (e.g., visual acuity results, cataract formation, development of advanced AMD), and morbidity and mortality.

11.2.1 Database Quality

Database quality will be maintained through a variety of analyses that target anomalies, delinquent data, and key-entry errors. A part of this process will be to analyze the frequency of errors according to type to determine if certain types of errors are recurrent. Modifications to the system will be made if the same types of errors occur frequently among the clinics. If errors are localized within a clinic, steps will be taken to resolve the problems by providing additional training for Clinical Center staff or modifying the AREDS Interactive Data Entry System (AIDES).

11.2.1.1 Duplicate and error checks. Although the AIDES is designed to prohibit duplicates, a check will be made periodically at the Coordinating Center to ensure that no undetected duplicates remain. Following this check, another check of the database will examine the individual fields and computed values within each record for illegal or conflicting entries. Variables that are in error or inconsistent with other data will be compared to an Anomaly Exception File.

The Anomaly Exception File is a means of documenting acceptable anomalies based on Participant Number and Visit Number. The Anomaly Exception File will be maintained by the Database Administrator at the Coordinating Center as a record of resolved queries. It contains the Registration Number, Visit Number, and form and field identifiers, as well as the reason for the exception and the date it was entered. A second date field is available if the exception has an expiration date.

11.2.1.2 Delinquent data. Delinquent data will be determined at the form level and the field level. Delinquent forms will be identified and compared to an exception file. All missing forms will be grouped by site and a report file will be generated for distribution to the appropriate Clinical Centers. A missing form will continue to be requested either until the data for the form are transmitted and integrated into the Coordinating Center's central master database or until an exception is granted and entered into the Missing Forms Exception File.

Fields also will be checked for values which indicate that they are missing and were not keyed into the form. Like the missing form and error/anomaly review, this program will identify the missing values by Registration Number, Visit Number, form, and variable. Reports which identify

missing values are generated by site and mailed to the Clinical Centers or Reading Center Coordinators. Missing values will continue to be reported until completed or until an exception is granted.

11.2.1.3 Key-entry errors. Although range checks will be made at the time of key entry to reduce the chance of careless errors in data entry, the accuracy of the data entered will be monitored by selecting a random sample of participant numbers and verifying the data entered into the system by comparing the original clinic record with the information in the database. A report summarizing the results will be submitted to the appropriate Clinical Center, with a copy to the Operations Committee. Methods for improving the problems identified will be explored and modifications to the AIDES will be considered.

11.2.1.4 Database integrity. The various components of the AIDES will be audited periodically for accuracy and completeness by requiring the Clinical Centers and the Reading Center to make copies of their database back up files. The files will be sent to the Coordinating Center to be compared, record-by-record and field-by-field, with the data in the central database at the Coordinating Center. Identified discrepancies will be resolved and corrected by the Clinic Monitor where possible. During the initial months of Phase II, each site will be asked to send their diskettes for an initial baseline audit. Subsequently, each site will submit a copy once a year, and an additional on site audit will be performed during the Protocol Review Visits.

Additionally, a sample of data records will be selected for comparison with original clinic records and the existence of all enrolled participants will be verified. This audit will be performed by the Protocol Monitor during Protocol Review Visits. Errors will be resolved with the Clinic Monitor where possible. The frequency of such errors will be tabulated and reported to the DSMC.

11.2.2 Operational Statistics

Analyses directed at monitoring the smooth and efficient operation of the study (e.g., the adequacy of participant enrollment, the completeness of data forms, the quality of the completed data forms, delays in completing data forms, numbers of missed visits, study dropouts) will be performed routinely. The reports of these analyses will help identify local problems that need to be resolved and indicate modifications that need to be made in the study procedures. Some of the reports which are likely to be generated include:

- ! Number of participants randomized, by clinic and month, with cumulative totals.
- ! Delay between completion of clinic visit and receipt of data at Coordinating Center, by clinic with average of clinic performance.
- ! Percentage of error-free data forms, by clinic and total.
- ! Numbers of missed visits, by clinic and visit and by total.
- ! Number of dropouts, by clinic and by total.
- ! Number of examinations performed by uncertified personnel.

11.2.3 Participant Characteristics

The characteristics of participants and study eyes will be analyzed according to the assigned intervention, AMD classification, and clinic in order to determine whether randomization succeeded in balancing the groups with respect to the following characteristics:

- ! Age, sex, race, etc
- ! Adherence with therapy
- ! Visual acuity
- ! Medication history
- ! Lens status

11.2.4 Outcome Variables, Morbidity, and Mortality

Outcome variables, morbidity, and mortality assessments will be performed as described in Section 3.1.5. These assessments will be prepared by the statisticians at the Coordinating Center for meetings of the DSMC. All statistical presentations of AREDS data will show the number of participants or eyes on which each statistical result is based (whether the result is a mean, a percentage, an incidence rate, or prevalence rate, etc). Standard errors, confidence limits, or other measures of sampling variability will also be shown.

11.3 REPORTING

A variety of scientific and administrative reports will be prepared for AREDS, such as:

- ! Adverse Experience Reports (AER) to the Food and Drug Administration, Bausch & Lomb, and DSMC
- ! Monthly reports for the Operations Committee, summarizing Clinical Center adherence to the study protocol
- ! Periodic reports on protocol adherence for Executive Committee and Technical Group meetings
- ! Semiannual reports on protocol adherence, data quality, and outcome results for the DSMC
- ! Protocol violation reports for the AREDS Project Officer, Study Chairperson, and Executive Committee
- ! Reports for scientific publication to be reviewed by the Editorial Committee.

11.3.1 Adverse Experience Reports Procedure

Clinical Centers are required to report adverse experiences to the Coordinating Center on the Adverse Experience Report Form. Each AER submitted to the Coordinating Center as a result of a serious event is forwarded to Bausch & Lomb for review and a decision is made concerning the need for further action. The prime consideration is whether the findings may affect the safety of participants enrolled in ongoing studies. If so, Bausch & Lomb takes immediate steps to notify the Study Chairman, the FDA, and the DSMC. In addition, monthly reports summarizing all AERs received will be distributed by the Coordinating Center to the Operations Committee and Bausch & Lomb.

11.3.1.1 Reports to the FDA. Bausch & Lomb submits several different types of reports to the FDA based on adverse experience data reported by investigators. The reports submitted are:

(1) Safety Reports

Safety Reports submitted to the FDA contain material on an adverse experience, detailing such information as: medical history, concomitant medications, outcome, relationship to study medication and occurrence of other similar adverse experiences on the study. Safety Reports are required for two types of adverse experiences:

- (a) **Three Days:** Regulations require that Bausch & Lomb notify the FDA by phone of deaths (within three days of notification) and of life-threatening adverse experiences which may possibly be related to use of study medication (immediately).
- (b) **Ten Days:** Bausch & Lomb must submit a written Safety Report to the FDA within 10 days of receipt of report for serious adverse experiences which are unexpected and may possibly be related to use of study medication.

(2) Information Reports

Occasionally an Information Report describing unusual or unique adverse experience is submitted to the FDA.

(3) Annual Reports

A brief report of the progress of the investigation will be submitted within 60 days of the anniversary date of the IND.

11.3.2 Reports to Operations Committee

The Coordinating Center will submit to the Operations Committee reports summarizing Clinical Center adherence to the study protocol and recruitment activities. These reports will include results of Protocol Review Telephone Calls, Protocol Review Visits, Clinical Center database quality and timeliness, and protocol violations. In addition, monthly reports for the Clinical Centers will be prepared to provide them with similar data. A newsletter will serve to update the participating clinics on the study enrollment, protocol modifications, all personnel changes, and will provide a

forum for circulating answers to protocol questions from the clinics. The newsletter will also serve to promote interest in the study.

11.3.3 Reports to Executive Committee and Technical Group

Protocol adherence reports will be prepared for periodic Executive Committee and Technical Group meetings. Copies will be forwarded to the AREDS Project Officer. These reports will provide operational data to the participating Clinical Centers and will serve to evaluate study progress. Outcome information will not be provided.

11.3.4 Reports to the Data and Safety Monitoring Committee

A comprehensive report will be prepared and submitted semiannually to the DSMC. Specific requirements for these reports are defined by the DSMC. The reports will be in the form of tables and graphic displays summarizing administrative, adverse experience, and other outcome data.

11.3.5 Protocol Violation Reports

Protocol violations will be monitored continuously. Such violations can occur for a variety of reasons, and many of these violations can be avoided, such as carelessness of a clinic to thoroughly screen a participant prior to entry, administrative errors in allocating dietary supplements, and missed visits due to inadequate participant/clinic communication. Timely identification of such problems can prevent future violations. All violations, regardless of cause, will be reported to the AREDS Project Officer, Study Chairperson, and Executive Committee.

11.3.6 Scientific Reports

After approval of a scientific report by the Analysis Planning Committee, the Coordinating Center's statisticians will assist AREDS investigators in preparing scientific publications. In collaborating with clinicians on publications, the statisticians can provide tabular and graphic presentations of data, as well as a description of the study methods and results.