

## Chapter 12

### QUALITY ENHANCEMENT

#### 12.1 INTRODUCTION

The principles of multicenter clinical studies that govern the AREDS quality enhancement program are:

- ! Uniform definitions
- ! Uniform criteria
- ! Uniform procedures
- ! Recruitment of adequate numbers of participants
- ! Maintaining complete follow up of all, or nearly all, participants.

The goal of the quality enhancement program is to maintain the scientific integrity of the study.

During a long-term multicenter study, many anomalies can occur that may impair the validity of the data collected and, thereby, the scientific integrity of the study. Among these are:

- ! Malfunctioning or improperly calibrated equipment
- ! Inadequately trained personnel performing study procedures
- ! Study personnel failing to perform procedures in the (standard) manner specified
- ! Study personnel forgetting to perform specified procedures
- ! Study personnel neglecting to record certain observations on the data forms
- ! Excessive waiting or other irritations suffered by participants
- ! Participants losing confidence in the clinic or its staff
- ! Failure of participants to appear for followup examinations.

The quality enhancement program for AREDS is similar to programs adopted in other multicenter studies<sup>1-4</sup> and is intended to prevent or minimize anomalies that may weaken the quality of the data collected because of missing or invalid observations.

The program is based on the following six principles:<sup>1,2</sup>

1. Standardized training and certification of clinic personnel in the conduct of study procedures (Chapter 9)
2. Responsibility and accountability of the personnel at the Clinical Centers, Coordinating Center, and Reading Center for implementing the study and maintaining the integrity of the data collected
3. Open lines of communication among the Coordinating Center, Clinical Centers, Reading Center, Drug Distribution Center, and Drug Company
4. Routine pilot testing of forms and procedures
5. Observation of clinic activities by external monitors who assess staff adherence to study procedures
6. Analysis of the quality of the data
7. Medical review of participant eligibility and outcome measurements (e.g., visual acuity and fundus photography) to assure adherence with protocol requirements.

## **12.2 RECRUITING ADEQUATE NUMBERS OF PARTICIPANTS**

A critical task for all clinical studies is the enrollment of adequate numbers of participants, a task that often proves to be more difficult than anticipated. A recruitment goal has been established for each AREDS Clinical Center (Section 3.1.3.6). Each Clinical Center will develop a written plan (Section 13.6) for meeting this recruitment goal and review this plan continually throughout recruitment in order to determine its effectiveness. If the center is not achieving its recruitment goal in a timely fashion, the plan may need to be modified.

## **12.3 PREVENTING DROPOUTS AND MISSED VISITS**

A primary objective of AREDS is to study the clinical course of AMD and cataract. To achieve this objective, it is essential that each participant be examined regularly at followup visits until the study is terminated or until the participant dies. Missing information can bias the results of the study. Although occasional missed visits, due to illness for example, cannot be prevented, the study could be invalid if there are many missed visits (for example, if numerous participants drop out). When data are incomplete, it is difficult to predict the direction of any bias resulting from the incompleteness. The only correct way to deal with missing information is not to have any.

Preventing dropouts and missed visits is a responsibility shared by the entire clinic staff, and this topic should be discussed frequently at staff meetings. When participants move to a location near another AREDS Clinical Center, efforts should be made to transfer them to that center (Section 13.10).

Clinic personnel can help prevent dropouts by doing the following:

- ! Receive each participant cordially when he or she arrives at the clinic.
- ! Explain to each participant, upon his or her arrival, the procedures he or she will undergo.
- ! Minimize waiting time and attend to each participant's comfort during waiting periods.
- ! Reschedule appointments, when necessary, in ample time so that the participant can revise his or her own schedule.
- ! Explain to each participant the reason for any unusual delay during a clinic visit. Apologies should be offered and every effort should be made to help the participant revise and meet bus or plane schedules, call relatives, and extend motel checkout times, etc.
- ! Promptly followup on all missed appointments. In some cases, a phone call from the Clinic Coordinator stressing the need for a followup examination may be enough. (Saying that "the protocol requires it" should never be given as a reason because it suggests that the participant's convenience is secondary to adhering to an unnecessarily rigid protocol.) Some participants will respond more favorably if they are called by an ophthalmologist at the clinic. Help in arranging transportation should be offered, including the payment of travel costs, if necessary. Specific guidelines for when payment will be offered should be developed because funds for covering transportation costs are severely limited and cannot be offered to all participants. Participants who are unable to visit the clinic during regular hours may be willing to visit during evenings or weekends, or may be better able to attend another AREDS Clinical Center. Being willing to see a participant at his or her convenience, even at the inconvenience of clinic staff, will demonstrate the importance placed on followup and may improve a participant's cooperation.
- ! In any trial of ten-plus years duration (particularly with an older study population such as AREDS), it is expected that continued follow-up will become more difficult as the study progresses. Infirmary, illness, institutionalization, and uncooperative families are some of the reasons given for the reluctance or inability of study participants to continue to visit the Clinical Center. However, it may be possible for clinic staff to gather some data on the participant's status by employing one or more of the following strategies:

1. If the participant is in a nursing home and unable to cooperate or tolerate an ophthalmologic examination, some data may be obtained from a social worker, nurse, or other institution employee.
2. Interview a dependable family member.
3. Obtain permission to speak with the participant's eye-care or other health-care provider.
4. Conduct a home- or health-care facility visit, if possible.

#### 12.3.1 Use of Outside Services for Locating Participants Lost to Follow-up

- ! Internet Services. The last known address and telephone number of many persons can be obtained through a locator service at URL [www.555-1212.com](http://www.555-1212.com). Staff can update information on participant contacts using the same service. Determining if a participant has died can often be accomplished by accessing the Social Security Death Index at URL [www.ancestry.com](http://www.ancestry.com).
- ! Funeral homes can, in some cases, provide copies of missing death certificates for legitimate purposes.
- ! Choice Point. The AREDS Coordinating Center has contracted with this locator service for Clinical Center personnel to use after all other reasonable efforts to contact participants have failed. Formerly called Equifax, the service is headquartered in Virginia and has located patients/participants in other clinical trials for both private industry and the National Institutes of Health. To initiate a search, clinic staff must complete an AREDS 'Study Subject Search Form'. The form is printed on Choice Point letterhead, and copies were distributed to each center in the spring of 1998; additional copies may be obtained from the Coordinating Center. Clinic staff must forward the completed form via fax *directly to Choice Point*. This is necessary to preserve the anonymity of study participants. After Choice Point receives a search request from a Clinical Center, they are authorized to spend up to three hours per participant in an attempt to obtain current contact information. Choice Point will then transmit any information obtained directly back to the Clinical Center that initiated the search. Choice Point will at no time attempt to contact the participant, family members, or alternate contacts. It is the responsibility of the Clinical Center to then use the information provided to contact participants in an effort to complete a study visit. Choice Point will invoice the AREDS Coordinating Center on a monthly basis for all searches conducted in the previous month, along with the number of searches requested by each Clinical Center. The invoices will be devoid of any personal data on study participants. Mr. Brandon Cosby, Choice Point Project Development Executive, is the primary contact for AREDS-related inquiries. Mr. Cosby may be contacted at: phone - (703) 749-9707, fax - (703) 821-8272.

## **12.4 INTERNAL CLINIC MONITORING**

### **12.4.1 Clinic Director**

Each Clinic Director is responsible for ensuring that all study procedures are adhered to in the clinic. He or she must spend adequate time at the clinic observing study procedures and regularly reviewing, one on one or in group meetings, various aspects of the study to resolve any problems that may arise.

Other clinic staff members are responsible for reporting to the Clinic Director any problems that could affect the quality of the data.

### **12.4.2 Clinic Monitor**

The Clinic Monitor designated by the Clinic Director is specifically responsible for reporting problems that have affected or can potentially affect the quality of the data collected. These problems are reported to the Clinic Director and to the Protocol Monitor at the Coordinating Center (Section 12.5).

The Clinic Monitor may be the Clinic Director, the Clinic Coordinator, or another staff member who is thoroughly familiar with the activities and equipment of the clinic and the AREDS Manual of Operations. The Clinic Monitor should maintain an up-to-date copy of the Manual of Operations and encourage all clinic personnel to consult it frequently.

The Clinic Monitor will receive regularly scheduled telephone calls from the Protocol Monitor at the Coordinating Center. These calls will follow a structured format, and the Clinic Monitor is responsible for following up on any actions that may be needed as a result of the call.

At meetings of the Technical Group, all Clinic Monitors will meet with the Protocol Monitor and Database Administrator from the Coordinating Center to discuss mutual problems.

## **12.5 EXTERNAL CLINIC MONITORING**

External clinic monitoring is performed by the Protocol Monitor, at the Coordinating Center. The Protocol Monitor collaborates with the Database Administrator at the Coordinating Center in the editing of data received by the Coordinating Center, places regularly scheduled telephone calls (Protocol Review Calls) to each Clinical Center, participates in periodic Protocol Review Visits to each Clinical Center, monitors the certification status of each Clinical Center, and reports findings periodically to the Operations Committee. Each of these functions is described more fully below.

### **12.5.1 Data Editing**

Data editing at the Coordinating Center, conducted under the direction of the Database Administrator, involves checking the data forms transmitted from the Clinical Centers to the

Coordinating Center for completeness, adherence to the Manual of Operations, and internal consistency. This editing is performed both manually and by computer. The computer edit generates "error messages" regarding incomplete, questionable, or inconsistent data.

Part of the editing process is to analyze the frequency of errors according to their type to determine if certain types of errors keep recurring. If they do, this information is communicated by the Protocol Monitor to the clinics concerned and suggestions for improvement are made. Another part of the editing process is to audit a sample of data. This audit is done by the Protocol Monitor who, during Protocol Review Visits, compares information in a clinic's participant charts with information transmitted to the Coordinating Center. Any discrepancies are resolved by discussion with the Clinic Monitor. A computerized database audit is also performed as described in Section 11.2.1.4.

### 12.5.2 Protocol Review Calls

The Protocol Monitor makes regularly scheduled Protocol Review Calls to each Clinic Monitor. Initially, these telephone calls are made monthly and gradually become less frequent. The calls follow a structured agenda that is sent in advance to the Clinic Monitors. The agenda includes the following:

- ! Staff changes and current or impending needs for training or certification
- ! Functioning and calibration of equipment
- ! Participant enrollment
- ! Satisfaction of participants with their visits to the clinic
- ! Satisfaction of staff with the working conditions
- ! Problems in meeting the requirements of the study
- ! Problems in completing data forms
- ! Problems in data processing.

These regularly scheduled telephone calls are designed to enhance positive communication. Rather than emphasizing errors made by the Clinical Center, which the Coordinating Center staff may do in other telephone calls, Protocol Review Calls give each Clinic Monitor the opportunity to report on the many ways in which the clinic is functioning properly and successfully.

The Protocol Monitor prepares for all Protocol Review Calls by reviewing the data received from a Clinical Center, information about any errors made by the center, the certification status of new staff members, notes from previous calls, and recent correspondence from the Clinical Center.

The Protocol Monitor and Database Administrator keep a log of telephone calls, correspondence, and site visits for each Clinical Center. The Protocol Review Calls are not a substitute for other telephone calls that may be needed to resolve problems as they occur. Such calls should be made as often as needed.

### 12.5.3 Protocol Review Visits

Each Clinical Center will be visited periodically by one staff member from the Coordinating Center, such as the Protocol Monitor, or by Coordinating Center staff and one or more other individuals, including members of the Executive Committee or DSMC and a technician or Clinic Coordinator from another clinic. The purpose of these visits is to exchange information, review the Clinical Center's operations, conduct a data audit (see Section 11.2.1.4) and discuss and resolve any problems encountered.

The visit should be arranged for a day on which one or more participant visits are scheduled so that the procedures of the clinic can be observed. One of the visitors also may have some of the tests or examinations performed on him or her. The agenda for each visit will be sent in advance to all personnel involved in the site visit.

## **12.6 QUALITY ASSESSMENT OF PHARMACEUTICAL MANUFACTURING AND LABELING**

The quality of pharmaceutical manufacturing and labeling will be monitored by submitting a random sample of numbered bottles containing the placebo or zinc or antioxidant supplements to the Central Laboratory. The Central Laboratory will perform on a limited basis, by techniques available in the Central Laboratory qualitative and semi-quantitative tests of samples of AREDS placebo and active study medication to confirm the content and consistency of study medication. This will serve as a secondary check of the quality of the study medication. This independent analysis will verify if the assigned intervention has been matched properly to the bottle numbers.

## **12.7 PARTICIPANT ADHERENCE ENHANCEMENT**

Good participant adherence with the study protocol is essential for the success of the study. The best way of improving participant adherence is for the clinic staff to develop a good relationship with the participant, to show interest in the participant, and to emphasize repeatedly the importance of taking all prescribed medications and following directions. The benefits of participating in the study will be explained to each participant prior to enrollment and periodically during followup. Tools for adherence to the study protocol will be developed by each Clinical Center. These tools should convey appreciation for the individual's participation in AREDS and may include birthday or other greeting cards, calendars indicating clinic appointments, and clinic informational pamphlets.

## 12.8 REFERENCES

1. Williams OD: A framework for the quality assurance of clinical data. *Clin Pharmacol Ther* 25 (No. 5, Part 2):700-702, 1979.
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3. Ferris FL, Ederer F: External monitoring in multiclinic trials: Applications from ophthalmologic studies. *Clin Pharmacol Ther* 25 (No. 5, Part 2):720-723, 1979.
4. Cassell GH, Ferris FL: Site visits in a multicenter ophthalmic trial. *Controlled Clin Trials* 5:251-262, 1984.