

## CHAPTER 6

### EXAMINATION SCHEDULE

#### 6.1 OVERVIEW OF SCHEDULE AND DESCRIPTION OF PARTICIPANT VISITS

This chapter presents the examination schedule for AREDS participants during Phase II, highlighting the important features of each examination. A list of AREDS forms and materials to be used by the Clinical Centers is also provided. Exhibit 6-1 provides an overview of visit requirements.

Candidates for the AREDS are examined for eligibility during the Qualifying Visit of Phase II, at which time a Qualification Number is assigned and photographs of the lens and retina are taken and forwarded to the Reading Center for final evaluation of eligibility, categorization of AMD, and assessment of iris color. Before randomization, participants will take part in a run-in period for at least 1 month and not more than 4 months during which they will receive a 1-month supply of placebo tablets (Trial Medication) for daily intake. Participants must sign an informed consent statement that describes their participation during the run-in period. The Reading Center will send the results of its eligibility evaluation and AMD categorization for each potential participant to the Coordinating Center which will notify the Clinical Center regarding eligibility. Participants who appear to be eligible will be asked to return to the Clinical Center for the Randomization Visit. Prior to randomization, a participant must sign a second informed consent statement that describes randomization and the responsibilities for continued participation in AREDS. The examining ophthalmologist will be asked to review the Reading Center's findings, examine the participant, and sign the Ophthalmologist Confirmation form if the findings of the examination are consistent with the Reading Center's assessment of the participant's AMD category.

Participants are randomized and assigned a bottle number when their eligibility information is entered into the AREDS Clinical Center Interactive Data Entry System (described in detail in the AREDS Data Management Handbook). Registered participants will be examined in the clinic at 6-month intervals. The examination requirements for all visits are given in Exhibit 6-2.

#### 6.2 QUALIFICATION

Exhibit 6-3 summarizes requirements between the Qualifying Visit and the Randomization Visit.

The examination for eligibility during the Qualifying Visit includes a measurement of visual acuity using Chart R or Charts 1 and 2, the taking of lens and fundus photographs, and review of personal and medical history. Participants who appear to be eligible during this visit will be assigned a Qualification Number. This number will be the Phase I registration number for participants enrolled during Phase I or the next sequential number for participants seen for the first time during Phase II.

Randomization must occur no more than 4 months after the date of the lens and fundus photographs, and at least one month after the date the Trial Medication was dispensed. If randomization does not occur during this time, participants must be requalified (Section 6.2.2).

### 6.2.1 Qualifying Visit

Exhibit 6-4 summarizes the sequence of events during the Qualifying Visit. When a Qualifying Visit is scheduled, the potential participant is mailed an AREDS medication bag and asked to use it to bring to the clinic all the medications and vitamin or mineral supplements he or she is taking. The participant may also be mailed the participant information booklet and the Food Frequency Questionnaire. The examination consists of:

- ! providing an explanation of AREDS and a copy of the participant information booklet (if not previously provided)
- ! signing of the Initial Informed Consent
- ! an interview (medical and ocular history)
- ! visual acuity examination using Chart R (manifest refraction and visual acuity examination using Charts 1 and 2 required if visual acuity score  $\leq 73$ )
- ! ocular examination
- ! fundus and lens photography (lens photography must be done at the Randomization Visit if it is not possible to obtain adequate quality lens photographs at the Qualifying Visit).
- ! blood sample (must be done at the Randomization Visit if it is not possible to obtain the sample at the Qualifying Visit).

Potential participants should be given:

- ! a self-administered Food Frequency Questionnaire (if not mailed prior to the Qualifying Visit). Completion of the questionnaire may be started in the clinic with the assistance of the coordinator, and may be finished during the Qualifying Visit, at home, or at the Randomization Visit
- ! the AREDS medication bag in which to bring their medications when they return to the clinic at the Randomization Visit
- ! two bottles of Trial Medication (and Centrum<sup>®</sup>, if applicable) and Instructions for Taking the Trial Medication
- ! a postcard to return to the clinic when the Trial Medication is stopped

- ! a card reminding the participants to bring the following when they return for the Randomization Visit:
- completed Food Frequency Questionnaire (if not completed during Qualifying Visit)
  - Trial Medication bottles
  - all medications and supplements he or she is currently taking.

If the Reading Center determines that the submitted photographs are not of suitable quality, retakes may be requested. Retake requests will be specific to the type of photograph (fundus, Neitz, and/or Topcon) and eye (right and/or left) required. Satisfactory photographs of the fundus are necessary prior to the Randomization Visit. Lens photographs may be retaken at the Randomization Visit; if the retakes are also unsatisfactory, a special retake visit must be scheduled as soon as possible.

The assessments and procedures during the Qualifying Visit are described below:

1. Participant information booklet and Initial Informed Consent

Before the Qualifying Visit begins the participant should be given the Participant Information Booklet to read and provided an opportunity to ask questions. An informed consent statement that describes the participant's responsibilities during the run-in period must be obtained before the Qualifying Visit examination begins. A final consent will be obtained when the potential participant returns for the Randomization Visit.

2. Medication bags

An AREDS medication bag may be mailed to participants before the Qualifying Visit with instructions to use the bag to bring to the clinic appropriately labelled containers of all medications and supplements being taken. The medication bag will be returned to the participant, so he or she may use the bag to bring the run-in medication bottles and any other medications to the clinic when returning for the Randomization Visit.

3. Medical History

The interview addresses aspects of medical and ocular history that may indicate ineligibility (STOP condition encountered). The Medical History section of the Qualification Form should be completed before undertaking further examination and evaluation.

4. Visual Acuity

A participant's current visual acuity is assessed using Visual Acuity Chart R as detailed in Chapter 7. The right eye is tested first followed by the left eye. If the visual acuity score in either eye is 73 letters or less, the participant must be refracted and retested using Charts 1 (right eye) and 2 (left eye).

5. Ocular Status

A participant's ocular status (evaluated by ocular examination) is evaluated for conditions that may make the participant ineligible for the study. (Section 7.4)

6. Food Frequency Questionnaire

A self-administered Food Frequency Questionnaire (FFQ) may be mailed to the participant prior to the Qualifying Visit. If not mailed, it will be given to the participant during the Qualifying Visit and must be completed prior to randomization. If time permits, participants should complete the entire FFQ at the clinic. However if scheduling problems arise, at least the first four pages of this questionnaire must be completed by the participant and reviewed by the Clinic Coordinator while the participant is at the Clinical Center. Participants demonstrating an understanding of the questionnaire may complete the remainder at home and return it at the Randomization Visit.

7. Blood Sample

A sample of blood will be taken during the Qualifying Visit for hematocrit testing, to be performed locally (Section 7.9). If it is not possible to obtain the sample at the Qualifying Visit, the sample may be taken at the Randomization Visit. Additional blood samples for other laboratory tests, to be performed at the Central Laboratory, are required for participating centers (see Chapter 18).

8. Fundus and Lens Photography

Good-quality color stereo photographs of the fundus of each eye are required (Chapter 8) for all participants before randomization. Retakes of unsatisfactory lens photographs may be obtained at the Randomization Visit, but if these are also unsatisfactory, a special retake visit must be scheduled. Beginning in year 2, lens and fundus photographs are repeated annually. As soon as the photographs are processed, they should be reviewed by clinic photographers for quality. If the quality is not adequate, the participant should be recalled to have photographs retaken. As soon as photographs of acceptable quality are obtained for both eyes, they should be labelled and assembled in plastic sheets as described in Chapter 8.

9. Run-in Trial Medication

Participants should be given

- ! AREDS Trial Medication Response card
- ! Reminder for Next Visit card
- ! Two bottles labeled Trial Medication: Week 1--Week 4 containing a 1-month supply of run-in supplements for daily intake
- ! Instructions for Taking the Trial Medication.

The participant should be asked to take 2 tablets in the morning with food and 2 tablets in the evening with food. Participants currently regularly supplementing with a multivitamin with or without minerals who wish to continue taking a supplement will be given Centrum®. Participants will be asked to mail the AREDS Trial Medication Response Card to the Clinical Center when the Trial Medication is stopped and return all bottles in the medication bag provided when they return for the Randomization Visit. Adherence to taking the run-in supplement will be assessed by estimated tablet counts if tablets remain, or date of completion of run-in supplement if the bottles are empty. (Section 7.13)

#### 10. Qualifying Visit Form

During the Qualifying Visit, the interview and examination results will be recorded on the Qualifying Visit form. The AREDS Qualifying Visit form contains a number of responses marked "STOP" to indicate that an exclusion criterion was encountered. The term "STOP condition" refers to these exclusion criteria. If a STOP condition is encountered, an Ineligibility for Phase II Randomization form should be completed.

#### 11. Mail Photographs

The date of photography is entered in the Photograph Shipment form in the AREDS Interactive Data Entry System. When a shipment is ready, the completed Photograph Shipping Manifest is printed and mailed with the photographs to the Reading Center. Shipments should be made weekly. The Reading Center, after determining the quality of the photographs and the potential participant's eligibility status, will notify the Coordinating Center of a potential participant's eligibility by completing and transmitting qualifying and summary grading records to the Coordinating Center.

Exhibit 6-5 summarizes the sequence of events following the Qualification Visit and prior to Randomization. Randomization must occur within 4 months of the date of the lens and fundus photographs. Photographs and visual acuity measurements are not required to be taken on the same day.

#### 6.2.2 Requalifying Visit

Participants must be requalified if (a) randomization does not occur within 4 months of the date of the lens and fundus photographs, or (b) at the Randomization Visit, the participant's visual acuity score in an eye without advanced AMD has dropped by 10 or more letters compared to the Qualifying Visit score. Requalification requires that the responses to each of the eligibility questions be verified. If participants are requalified due to expiration of the time period for photographs, only the outdated photographs (eg lens or fundus) must be reperformed. If only lens photographs are outdated, the photographs may be taken and the participant randomized on the same day. If participants are requalified due to a decrease in visual acuity, both fundus and lens photographs must be retaken. The Visual Acuity score measured using Charts 1 and 2 becomes the participant's Qualifying Visit visual acuity score. Participants being requalified need not go through another run-

in. The participant may be asked to return for the Randomization Visit as soon as the Reading Center assessment of the photographs has been made.

### **6.3 RANDOMIZATION VISIT**

Exhibit 6-6 summarizes the sequence of events during the Randomization Visit. Participants will be asked to return to the clinic for randomization when the Coordinating Center informs the Clinical Center of randomization clearance. Clinical Centers will be informed of the status of each participant awaiting randomization by generating a Pending Randomization Report (Appendix C). Registration and randomization in Phase II takes place only after the AREDS Interactive Data Entry System confirms eligibility and assigns a sequence number and a bottle number. Bottle numbers will be assigned by the computer from previously prepared randomization lists that are stratified by clinic and AMD Category 1 versus 2, 3 or 4. The sequence number indicates how many participants have been randomized within a stratum. The randomization lists are fully encrypted and, if tampered with, will result in the disablement of the AREDS Interactive Data Entry System. The master randomization list for each center is maintained at the Coordinating Center. Periodic audits are performed to ensure the continued integrity of the randomization process. In the unlikely event of computer failure, eligibility screening and randomization may be performed by calling the Coordinating Center Monday through Friday from 9:00 a.m. to 5:00 p.m. Eastern Time.

Participants in AMD Category 1 will be randomized between placebo and antioxidants, and participants in AMD Categories 2, 3, and 4 will be randomized among placebo, antioxidants, zinc, and antioxidants and zinc. A brief description of the Randomization Visit is as follows:

1. Final Informed Consent

An informed consent statement that describes randomization and responsibilities for continued participation in AREDS must be obtained before the Randomization Visit begins.

2. Ophthalmologist Confirmation of Reading Center Findings

The examining ophthalmologist will be asked to examine the participant and review the Reading Center's findings. If the findings of the eye examination are consistent with the Reading Center's assessment of the participant's AMD category, he or she may sign the Ophthalmologist Confirmation form. If the results of the ophthalmologist's examination is inconsistent with the Reading Center's assessment, the ophthalmologist may order retakes of all eligibility fundus photographs and submit them to the Reading Center for evaluation. If the ophthalmologist and the Reading Center agree that the participant is in Category 2, 3, or 4 (but not on which of the three categories), the participant may be randomized following retakes of the photographs and prior to Reading Center reevaluation. If the two parties disagree on whether the participant is in Category 2, 3, or 4 or in Category 1, then the participant may not be randomized but may be requalified. The Coordinating Center should be notified any time a discrepancy occurs. If indicated, the Reading Center will modify the data record, notifying the Coordinating Center of the change, and transmit the

correct data. The Clinical Center will receive the modified data and print a new Ophthalmologist Confirmation form for signature. (Exhibit 6-7)

3. Determination of Adherence

Participants will be asked to return the bottles of run-in medication dispensed during the Qualifying Visit. Adherence will be assessed by estimating the number of tablets remaining of those dispensed. Participants who appear to have been unable or unwilling to take at least 75 percent of their tablets will be ineligible. The AREDS Interactive Data Entry System will calculate adherence based on the number of days between the date the participant began the tablets and the day the run-in tablets were stopped and the estimated number of tablets remaining of those dispensed. Adjustments for days stopped due to illness or bottle misplacement will be made.

4. Manifest Refraction and Visual Acuity

A participant's manifest refraction and current visual acuity (Charts 1 and 2) is assessed as detailed in Chapter 7. After refraction, the visual acuity of the right eye is tested first using Chart 1, followed by the left eye using Chart 2. If the visual acuity score has dropped by 10 or more letters in either eye compared to the measurements during the Qualifying Visit, the participant must be requalified. If the drop in visual acuity score occurs in an eye with advanced AMD or in an eye with visual acuity < 74 letters due to AMD, requalification is not necessary.

5. Intraocular Pressure (IOP)

The IOP of both eyes will be measured prior to randomization. If photography must be performed after the measurement of intraocular pressure, the following precautions should be taken to ensure that disturbance of the cornea does not compromise photographic quality.

- (1) The tip of the tonometer should not be moved excessively while in contact with the cornea (ie, if it must be repositioned, it should be pulled back first), and
- (2) After tonometry the participant should be reminded to blink frequently to avoid drying of the cornea, and if necessary the cornea should be irrigated.

6. Blood Sample

A sample of blood will be taken during the Randomization Visit if blood was not obtained during the Qualifying Visit for hematocrit testing or additional analyses (see Chapter 18).

7. Food Frequency Questionnaire and 24-hour recall

Food Frequency Questionnaires not completed at the Qualifying Visit must be completed prior to randomization. In addition, 200 participants from 3 of the AREDS Clinical Centers obtaining participant blood specimens (Johns Hopkins Medical Institute, National Eye Institute, and Devers Eye Institute) will be asked to participate in a dietary recall interview (24-hour recall) conducted by telephone by a nutrition interviewer. Potential participants in this 24-hour recall are randomly selected by the Coordinating Center. Selection is indicated on the Pending Randomization report. Participants will be asked to sign a consent form prior to participating in the 24-hour recall (see Section 7.7). If consent is obtained, 2 interviews will be conducted; the first about 2 weeks after randomization, and the second about 6 months later.

8. Assignment of Bottle Number and Sequence Number

Two-digit bottle numbers (01-50) and a seven-character sequence number are assigned by the computer after the Randomization form is successfully completed. These numbers are recorded on the Randomization Log by the Coordinator (Appendix C). The first three characters of the sequence number identify how many participants within the center have been randomized. The next character identifies the stratum (A: AMD Category 1 and B: AMD Category 2,3, or 4). The final 3 characters identify how many participants have been randomized within the stratum.

9. Baseline Interview

A risk-factor interview will be conducted by an AREDS Clinical Center staff member with the participant during the Randomization Visit. The interview will include a personal and medical history, medication use, and measurements of height, weight, and blood pressure.

10. Distribution of Study Medications

Participants will be provided with a supply of study medications by the Clinic Coordinator in the AREDS tote box. The supply will be sufficient to provide the participant with enough medication to take until he or she returns for the next study visit (Section 7.12.2). The bottles will be identified with the bottle number assigned at randomization and will be labeled "Study Medication." Participants currently supplementing with a multivitamin with or without minerals who wish to continue to supplement with a multivitamin and mineral tablet will be provided with Centrum® and will be reminded not to take other "nonstudy" multivitamins or extra supplements containing the nutrients used in AREDS. Participants will be given (1) Instructions for Taking the Study Medication and (2) Reminder for Followup Visit. A Supplementation Record and Adherence Worksheet must be completed by the Coordinator. (Appendix C)

## 6.4 FOLLOWUP VISITS

An overview of the followup visit schedule and sequence of procedures to be performed is provided in Exhibit 6-8.

Participants will be asked to return for a followup examination every 6 months after randomization. The followup period begins on the day of randomization, and the timing of followup visits is based on that date. After randomization, the AREDS Interactive Data Entry System will generate a participant's Appointment Schedule (Appendix C) listing the target dates and time windows for study visits (Section 6.5). Every effort should be made to conduct the study visit as close to the target date as possible and before the expiration of the time window.

If a visit is not conducted within the allowable time window, it will be designated as a **missed visit**. If any part of a visit is conducted within the allowable time window but the entire visit is not completed, it will be designated as an **incomplete visit**. AREDS data forms (Appendix C) will be completed and transmitted to the Coordinating Center following every visit.

Supplements will be dispensed at each study visit such that each participant has at least a 6-month supply available (Section 7.12). A record of supplements dispensed will be maintained by completing the Supplementation Record and Adherence Worksheet.

### 6.4.1 Nonannual Study Visits

Information to be collected at Nonannual Visits includes visual acuity, IOP, lens and fundus examination, ocular and medical history, hospitalization reports, supplementation problems, protocol anomalies, and adherence assessment. Event photographs may be required to document reasons for visual acuity decrease. The need for event photographs due to a decrease in visual acuity will be determined using the Change in Visual Acuity Worksheet to be generated by the Clinic Coordinator prior to each Nonannual Visit. If the visual acuity score has decreased 10 or more letters from the score at the Randomization Visit, a complete manifest refraction must be performed for documentation of a first event in an eye. If, after refraction, the visual acuity score is 10 or more letters below the score obtained at the Randomization Visit, event photographs (fundus and lens) will be required (Exhibit 6-9). One set of event photographs is required for each eye to document the first decrease in visual acuity by 10 or more letters for that eye. Event photographs are required for all eyes regardless of AMD status at study entry. Subsequent decreases do not require manifest refraction or event photographs. If photography must be performed after the measurement of intraocular pressure, the following precautions should be taken to ensure that disturbance of the cornea does not compromise photographic quality.

- (1) The tip of the tonometer should not be moved excessively while in contact with the cornea (i.e., if it must be repositioned, it should be pulled back first), and
- (2) After tonometry the participant should be reminded to blink frequently to avoid drying of the cornea, and if necessary the cornea should be irrigated.

Supplement bottles dispensed at the last study visit will be collected and a new supply issued; an adherence assessment will be made by estimated tablet count, and a Supplementation Record and Adherence Worksheet will be completed. Returned bottles that have not been opened may be redispensed to the same participant. Tablets from partially full bottles must be disposed of in accordance with the medical waste procedures locally required.

#### 6.4.2 Annual Study Visits

Information about important events occurring between study visits (e.g., ocular trauma, ocular surgery, or the development of major systemic diseases) will be collected as part of the Annual Visit form.

A complete manifest refraction and visual acuity measurement using Charts 1 and 2 are required at Annual Visits, as well as a fundus examination, and ocular and medical history. Fundus and lens photographs are taken at each Annual Visit with the exception of the first Annual Visit. Fundus and lens photographs are required at the first Annual Visit if, for the first time, the visual acuity has dropped by 10 or more letters compared to the visual acuity obtained at randomization. Photographs of the lens (Neitz retroilluminated anterior and posterior, Topcon slit lamp and Zeiss stereoscopic red reflex photographs) are required of both eyes of a sample of participants graded by the Reading Center as having any PSC opacities (>.1% involvement) in at least one eye in the Qualifying Visit photographs. Neitz, Topcon, and red reflex photographs of aphakic or pseudophakic eyes need not be taken. During follow-up, retakes will be requested when photographs are evaluated as less than borderline, and explanatory factors such as media opacity are not noted. These may be obtained at a specially scheduled photography session if convenient, otherwise at the next scheduled visit. If retakes are requested, Clinical Center staff should use their discretion as to whether a request to the participant for repeat photographs will jeopardize that participant's cooperation with the study. Other reports required at Annual Visits when applicable include hospitalization, adverse experience, and protocol anomaly. Supplement bottles dispensed at the last study visit will be collected and a new supply issued; an adherence assessment will be made by estimated tablet count, and a Supplementation Record and Adherence Worksheet will be completed. Returned bottles which have not been opened may be redispensed to the same participant. Tablets from partially full bottles must be disposed of in accordance with the medical waste procedures locally required. All clinics will be required to take blood samples for local hematocrit assessment. Additional blood samples for all participants will be required for participating centers. These samples will be used to assess potential toxicity and adherence (Chapter 18).

### 6.5 GENETIC SPECIMENS

AREDS participants will be asked for consent to provide an additional blood sample to be used to create an immortalized cell line for inclusion in genetic ancillary studies. These cell lines will form a repository that will be maintained at the central laboratory. Specimens may be used for studies of AMD and cataract following completion of approval procedures described in Section 5.7.2.4.

## **6.6 STUDY VISIT WINDOWS**

Exhibit 6-10 provides target dates and time windows for the completion of study visits. Every effort should be made to conduct study visits as close to the target date as possible and before the expiration of the time window.

## **6.7 MISSED VISITS AND INACTIVE PARTICIPANTS**

If a participant misses a scheduled examination, staff of the Clinical Center should contact the participant to reschedule the examination prior to the end of the time window in which the examination may be completed (Chapter 12). If the participant is unable to complete a scheduled followup examination within the acceptable time window, a Missed Visit form (Appendix C) for the visit is completed and transmitted to the Coordinating Center to indicate that the information from the scheduled examination is unavailable.

If an Annual Visit is missed, photographs must be taken at the next Nonannual Visit. If the participant is contacted by telephone, any adverse experiences, hospitalizations, or other information available should be recorded on the appropriate study forms.

For participants who have died, a Death Report form (Appendix C) should be completed and transmitted to the Coordinating Center along with a death certificate, if obtained.

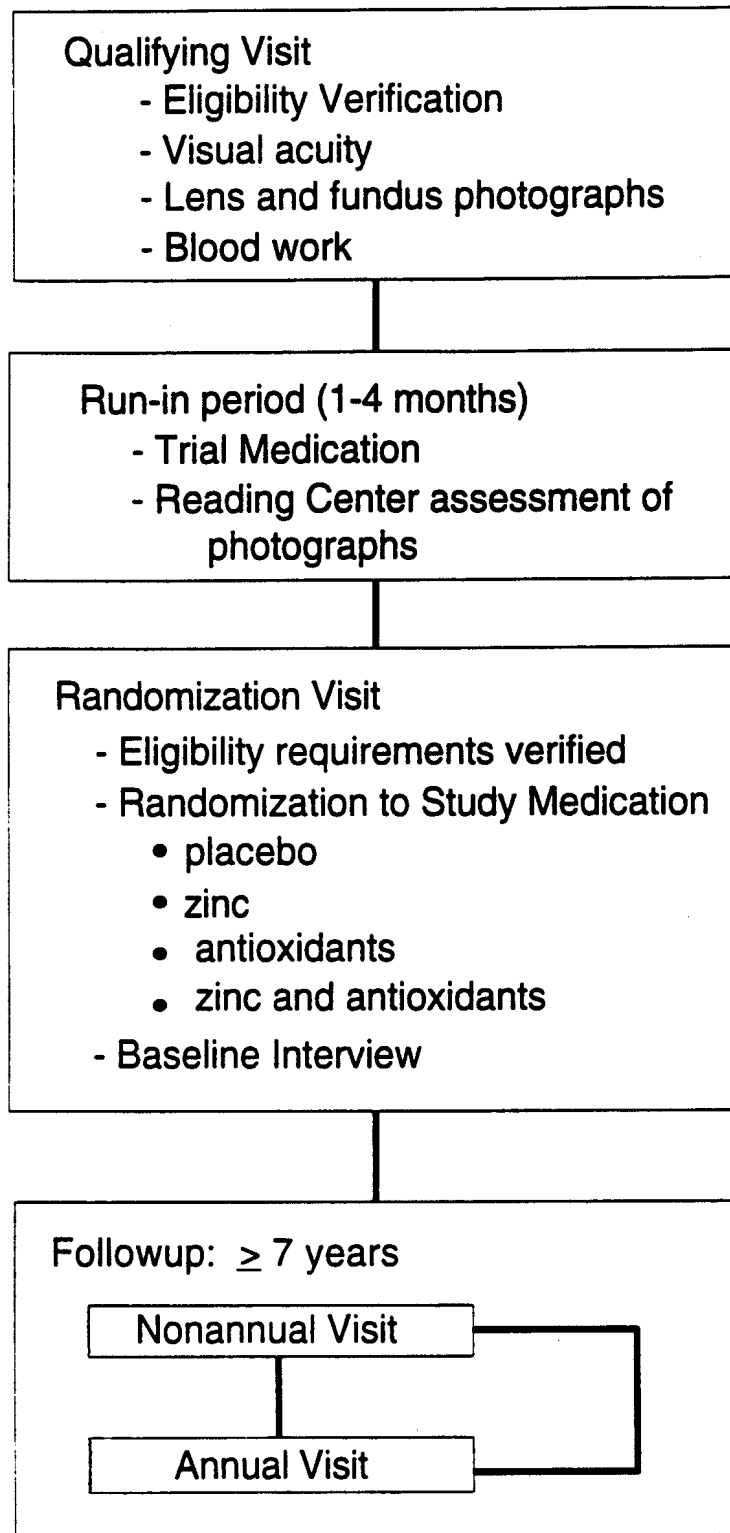
For participants who are otherwise unable to visit their Clinical Center, see Section 7.16 regarding examination at other clinics or at home.

## **6.8 DESCRIPTION OF CLINICAL STUDY FORMS AND MATERIALS**

A listing of AREDS forms, worksheets, reports, and materials available at the Clinical Centers is provided in Exhibit 6-11. In general all forms will be key-processed at the Clinical Centers. The Food Frequency Questionnaire will be mailed to the Coordinating Center following the Randomization Visit. A list of reports to be generated by the Clinical Centers is also provided in Exhibit 6-11. Detailed instructions for the use of the AREDS forms and reports are provided in the Data Management Handbook.

All paper forms and worksheets for the AREDS must be stored in a secure location and may not be destroyed. All visual acuity worksheets should be stored on site. Nonannual and Annual Visit Followup forms may be stored off-site, only after a new visit has occurred. That is, the first Nonannual Visit Followup form will be kept on-site until the second Nonannual Visit Followup is completed, and so on. Following the new visit, the forms from the previous visit may be placed in a secure storage facility off-site. When Clinical Center staff make corrections to the data, such changes will be made to the computer data record and need not be made on the paper worksheet or form. Documentation of the old value, the new value, the person making the change, and the date of the change will be monitored by the Coordinating Center via the computer system. Records of these changes will be maintained by the Coordinating Center.

**Exhibit 6-1. OVERVIEW OF STUDY VISITS**



**Exhibit 6-2. PHASE II PARTICIPANT EXAMINATION REQUIREMENTS**

Procedure	Qualifying	Randomization <sup>1</sup>	6-Month study visits	
			Nonannual	Annual
Initial Informed Consent/Registration	x			
Refraction	x <sup>2</sup>	x	x <sup>4</sup>	x
Visual Acuity	x (Chart R) <sup>2</sup>	x (Charts 1 and 2) <sup>3</sup>	x <sup>4</sup>	x
Fundus Examination	x	x	x	x
Ocular History	x		x	
Medical History	x		x	x
Blood Specimen	x	or x		x
Fundus and Lens Photographs	x		x <sup>5</sup>	x <sup>6</sup>
Intraocular Pressure		x	x	
Final Informed Consent		x		
Risk Factor Interview		x		
Adherence Assessment		x	x	x
Food Frequency	x	or x		x <sup>7</sup>
Final Registration and Randomization		x		
Sunlight Exposure Questionnaire			x <sup>8</sup>	x <sup>8</sup>
Visual Function Questionnaire			x <sup>9</sup>	x <sup>9</sup>

<sup>1</sup> Randomization must occur within 4 months of the date of the lens and fundus photographs

<sup>2</sup> Refraction and visual acuity (Charts 1 and 2) required only if visual acuity score (Chart R) is 73 or less in one or both eyes.

<sup>3</sup> If the visual acuity score has decreased by 10 or more since the Qualifying Visit, the participant must be requalified.

<sup>4</sup> Refraction and visual acuity (Charts 1 and 2) required only if vision drops by 10 letters (Chart R) compared to Randomization Visit score.

<sup>5</sup> Required if 10-letter drop (Charts 1 and 2) in visual acuity score from Randomization Visit score.

<sup>6</sup> Not required at first Annual Visit unless visual acuity has dropped by 10 or more letters from the Randomization Visit visual acuity score. Lens photos required if PSC opacity present at baseline for a sample of participants.

<sup>7</sup> Readministered at approximately 5 years.

<sup>8</sup> One visit only.

<sup>9</sup> Administered multiple times. Specific study visit dependent on first administration. See Section 7.21.2

**Exhibit 6-3. PHASE II QUALIFICATION AND RANDOMIZATION OVERVIEW**

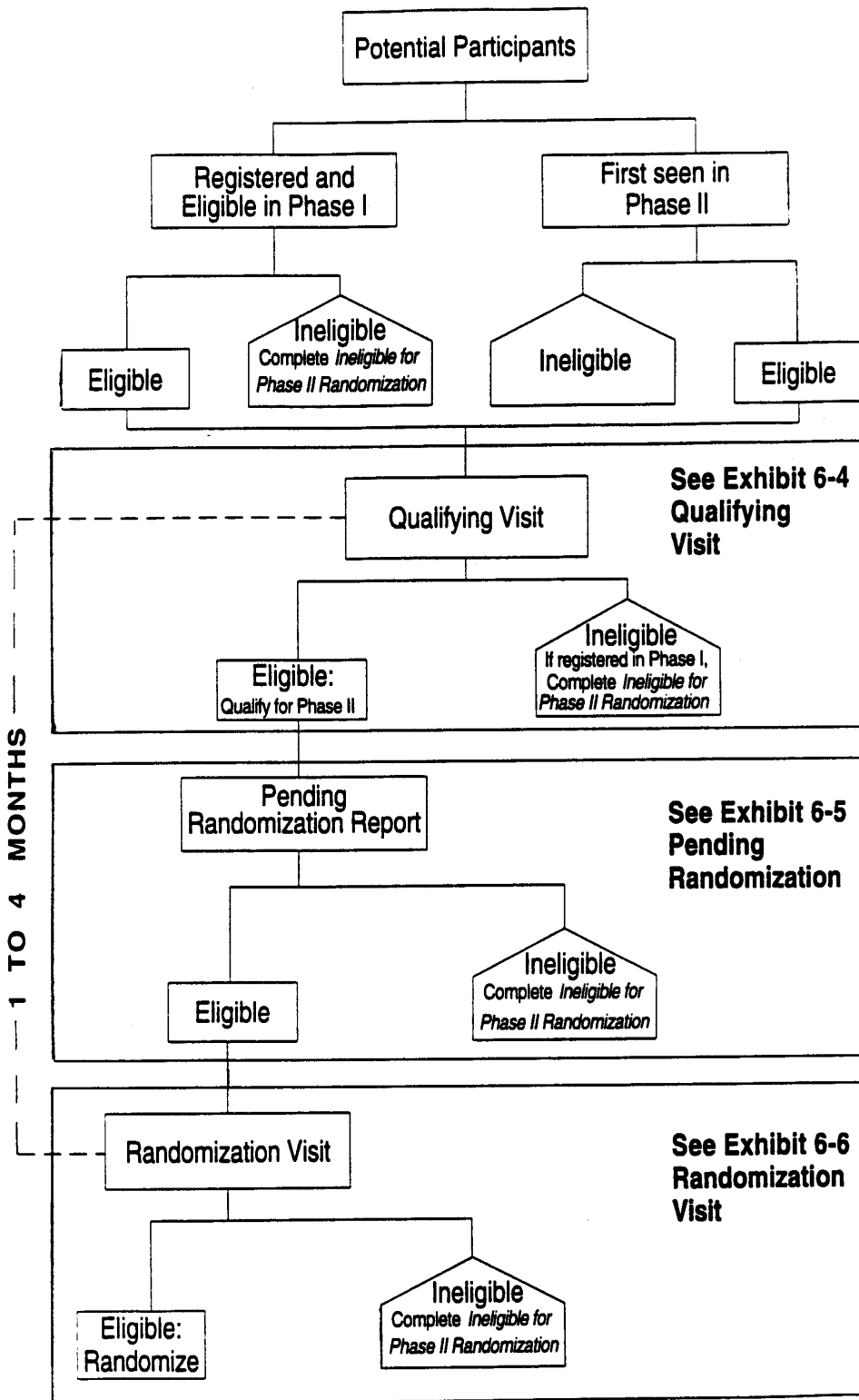


Exhibit 6-4. QUALIFYING VISIT SEQUENCE OF EVENTS

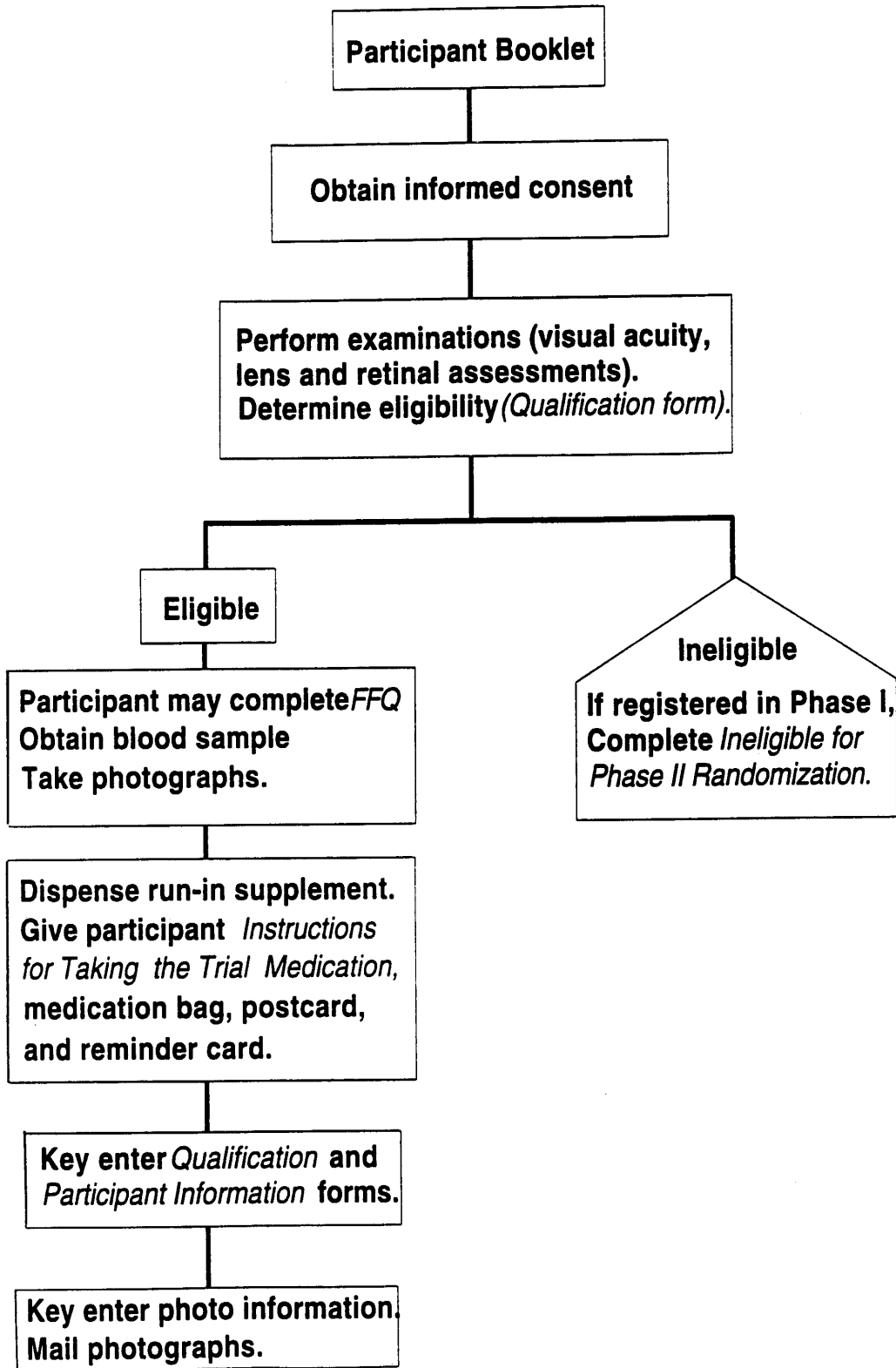
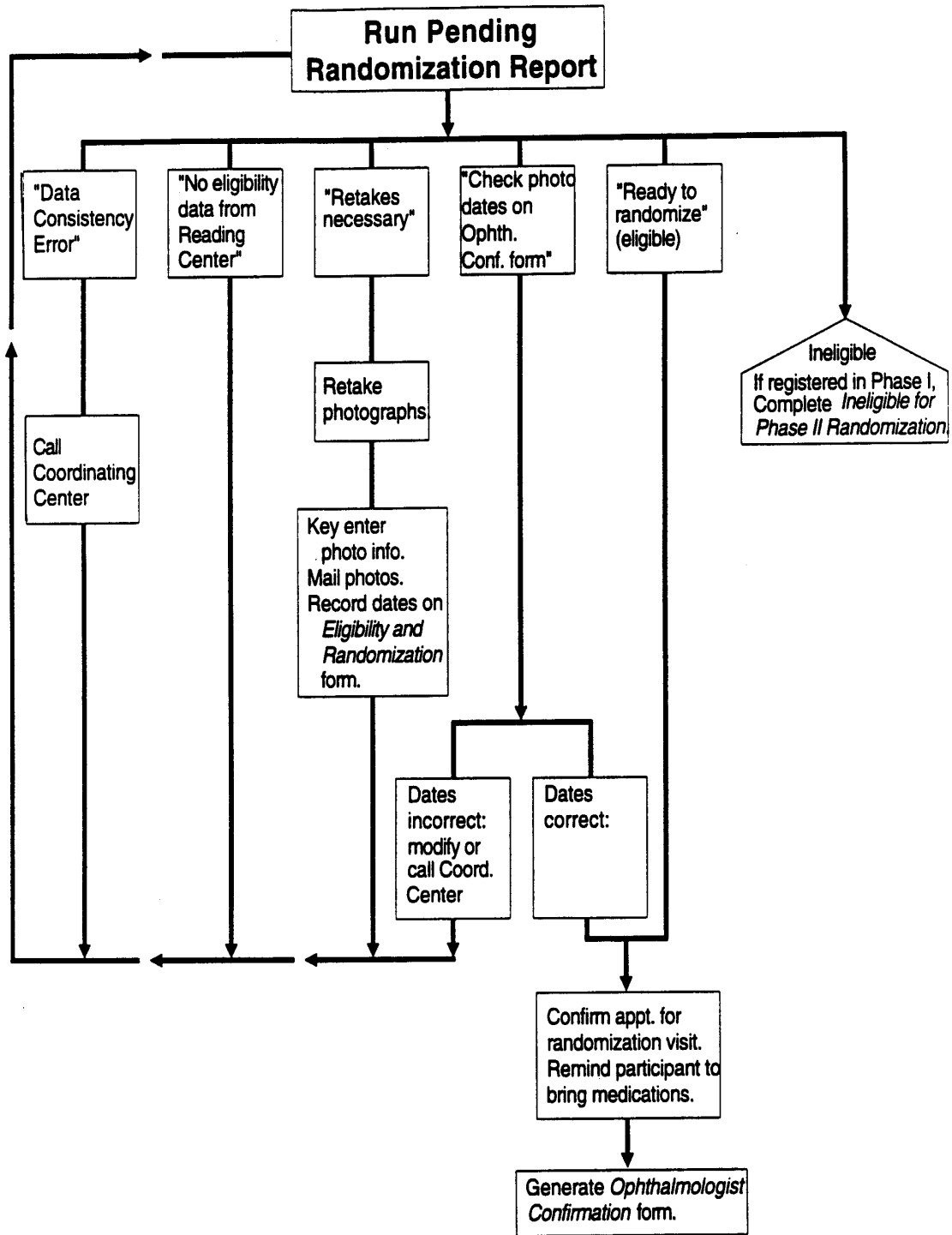
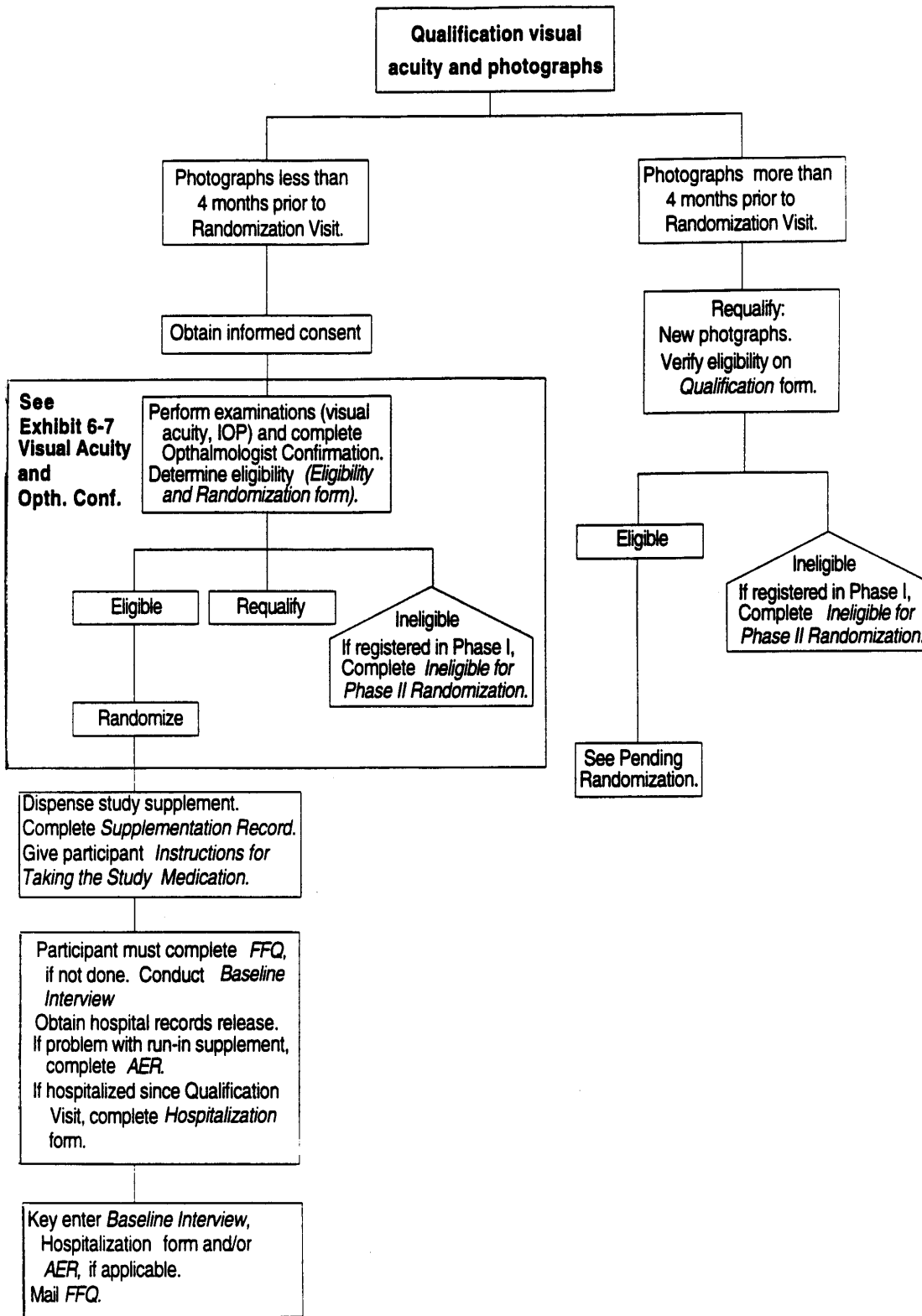


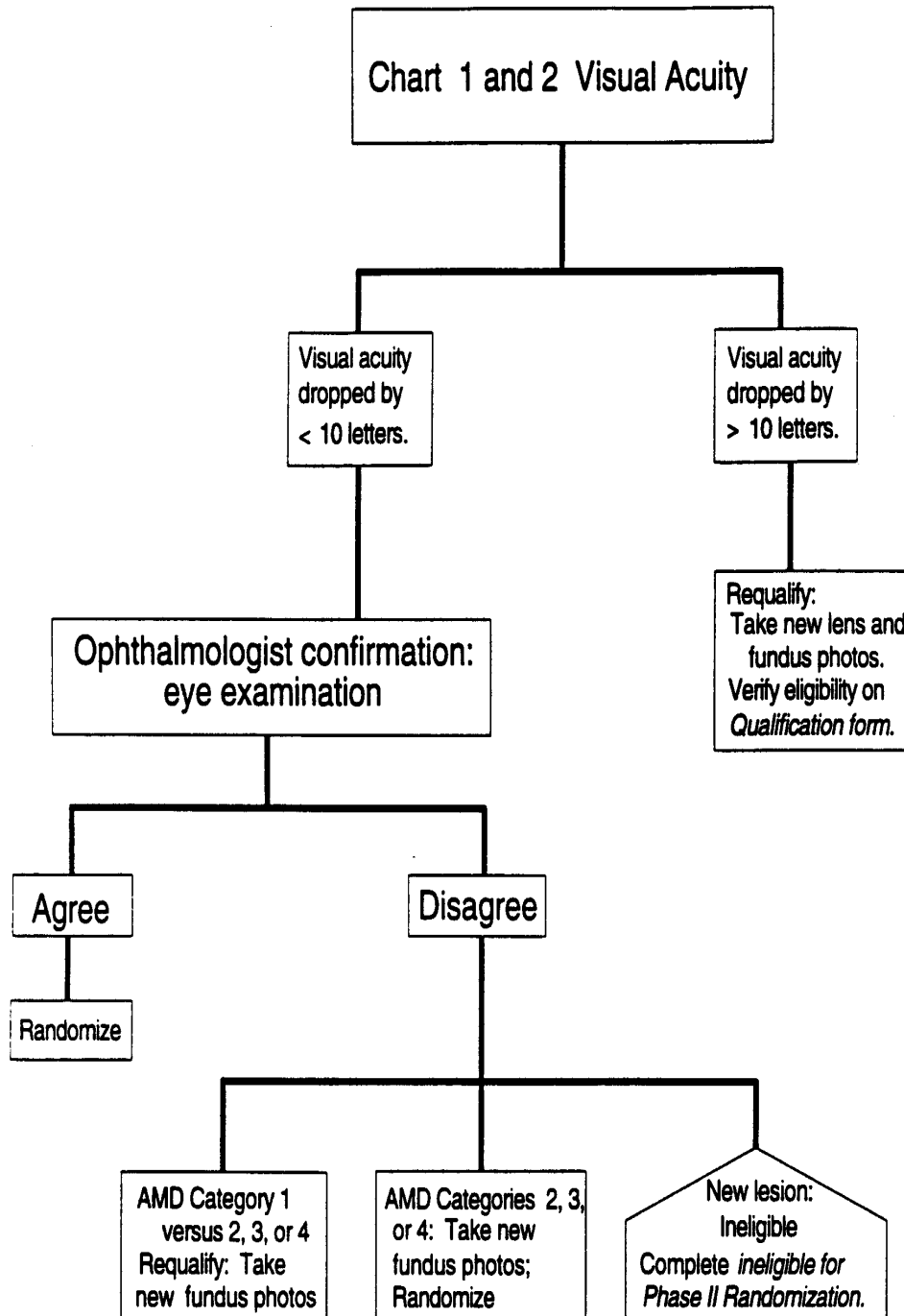
Exhibit 6-5. PENDING RANDOMIZATION SEQUENCE OF EVENTS



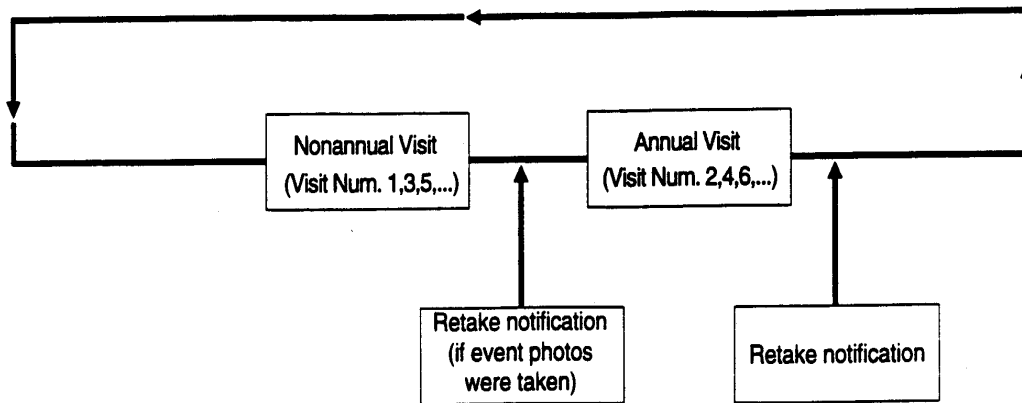
**Exhibit 6-6. RANDOMIZATION VISIT SEQUENCE OF EVENTS**



**Exhibit 6-7. OPHTHALMOLOGIST CONFIRMATION AND VISUAL ACUITY SEQUENCE OF EVENTS**



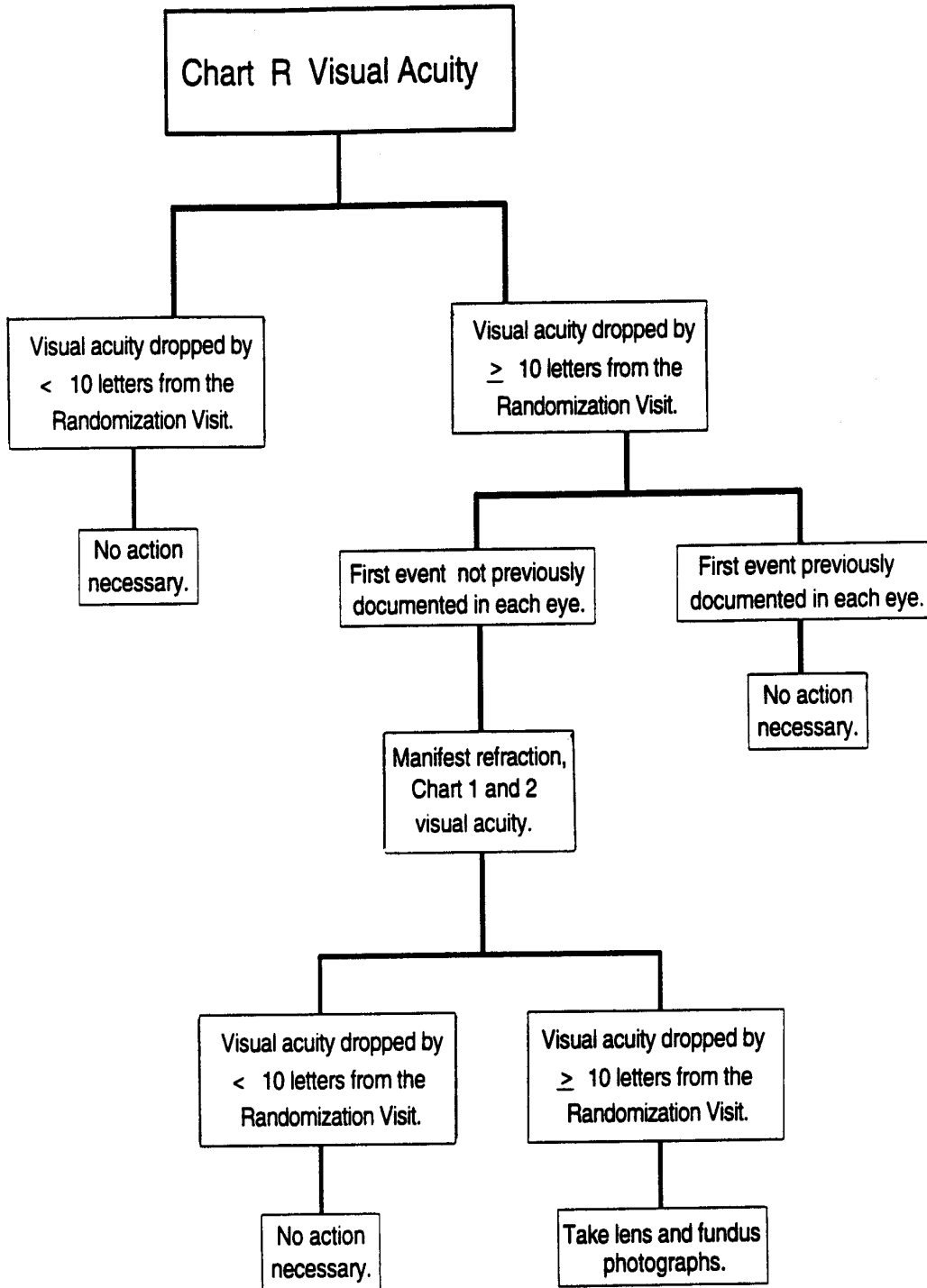
**Exhibit 6-8. FOLLOW-UP SEQUENCE AND PROCEDURES FOR PHASE II**



Nonannual Visit
<p>Complete Nonannual Visit Followup form or Missed Visit form.</p> <p>Visual Acuity (follow instructions on Change in VA Worksheet).</p> <p>Photos (if drop in visual acuity, or missed annual visit)</p> <p>Eye examination, IOP.</p> <p>If problem with supplement, complete AER.</p> <p>If protocol anomaly, complete Protocol Anomaly form.</p> <p>If hospitalized since last study visit or randomization, complete Hospitalization form.</p> <p>Collect supplement bottles.</p> <p>Dispense supplement and complete Supplementation Record and Adherence Worksheet.</p> <p>Schedule appointment for next Annual Visit (optional).</p>

Annual Visit
<p>Complete Annual Visit Followup form or Missed Visit form.</p> <p>Manifest refraction and Chart 1,2 Visual Acuity</p> <p>Take photographs. **</p> <p>Eye examination (no IOP).</p> <p>If problem with supplement, complete AER.</p> <p>If protocol anomaly, complete Protocol Anomaly form.</p> <p>If hospitalized since last study visit, complete Hospitalization form.</p> <p>Collect supplement bottles.</p> <p>Dispense supplement and complete Supplementation Record and Adherence Worksheet.</p> <p>Update signature on Release of Medical Records, if necessary.</p> <p>Schedule appointment for next Nonannual Visit (optional).</p> <p>** Unless first annual visit, no visual acuity drop, and participant not selected for PSC photograph</p>

Exhibit 6-9. NON-ANNUAL VISIT VISUAL ACUITY SEQUENCE OF EVENTS



**Exhibit 6-10. SCHEDULE AND TIME WINDOWS FOR AREDS STUDY VISITS**

STUDY VISIT		OPTIMAL TIME	MINIMUM TIME SINCE LAST VISIT	TIME WINDOW
Qualifying (QUA)		NA	NA	NA
Randomization (RA)		1 month	1 month post-QUA	1 month to 4 months post-QUA
Visit No.	MONTHS AFTER RANDOMIZATION	OPTIMAL TIME AFTER RANDOMIZATION	MINIMUM TIME SINCE LAST VISIT	TIME WINDOW {FROM RANDOMIZATION}
1	6-mo visit	6 mo	3 mo	3 - 9 mo (92-274 days)
2	12-mo visit	12 mo	3 mo	10-15 mo (275-457 days)
3	18-mo visit	18 mo	3 mo	16-21 mo (458-639 days)
4	24-mo visit	24 mo	3 mo	22-27 mo (640-822 days)
5	30-mo visit	30 mo	3 mo	28-33 mo (823-1,005 days)
6	36-mo visit	36 mo	3 mo	34-39 mo (1,006-1,187 days)
7	42-mo visit	42 mo	3 mo	40-45 mo (1,188-1,370 days)
8	48-mo visit	48 mo	3 mo	46-51 mo (1,371-1,552 days)
9	54-mo visit	54 mo	3 mo	52-57 mo (1,553-1,735 days)
10	60-mo visit	60 mo	3 mo	58-63 mo (1,736-1,918 days)
11	66-mo visit	66 mo	3 mo	64-69 mo (1,919-2,100 days)
12	72-mo visit	72 mo	3 mo	70-75 mo (2,101-2,283 days)
13	78-mo visit	78 mo	3 mo	76-81 mo (2,284-2,466 days)
14	84-mo visit	84 mo	3 mo	82-87 mo (2,467-2,648 days)
15	90-mo visit	90 mo	3 mo	88-93 mo (2,649-2,831 days)
16	96-mo visit	96 mo	3 mo	94-99 mo (2,832-3,014 days)

## Exhibit 6-11. AREDS PHASE II FORM AND REPORT INVENTORY (To be completed by Clinical Centers)

### FORMS AND WORKSHEETS

1. Qualification	23. Participant Screening
2. Photograph Shipment Form	24. Blood Drawing Questionnaire
3. Photograph Shipping Manifest *	25. Supply Order Form +
4. Specimen Shipping Manifest +	26. Refraction Log **
5. Study Supplement Order Form *	27. Supplemental Baseline Medication Worksheet **
6. Participant Information	28. Run-in Response Card ****
7. Food Frequency Questionnaire and Shipping Log **	29. Undispensed Study Medication
8. Ineligibility for Phase II Randomization	30. Vitamin Supplementation
9. Adverse Experience Report	31. Ancillary Blood Drawing
10. Death Report	32. Collaborating Physician ***
11. Ophthalmologist Confirmation *	33. Home Visit ***
12. Eligibility and Randomization	34. Parallel Studies Information
13. Change in Visual Acuity Worksheet **	35. Followup Interview
14. Randomization Log **	36. Genetics Blood Drawing Form ****
15. Baseline Interview	37. Genetics Specimen Submission ****
16. Release of Medical Records & Sample Cover Letter **	38. Genetics Clinical Center Specimen Log
17. Supplementation Record and Adherence Worksheet	39. Genetics CDC Shipping Manifest
18. Nonannual Visit Followup	40. Genetics Family History Form
19. Annual Visit Followup	41. Genetics-Participant Approval of Blood Sample Use
20. Protocol Anomaly	42. Sunlight Exposure Questionnaire
21. Missed Visit	43. Visual Function Questionnaire
22. Hospitalization	44. Collaborating Physician Supplemental Information Worksheet

### REPORTS

1. Pending Randomization Report	9. Explanation/Strategy for Supplementation Report
2. Confirmation of Randomization	10. Laboratory Alert Values for Hematocrit and Total Serum Cholesterol Report
3. Participant Appointment Schedule	11. Supplements Required
4. Appointment Scheduling	12. PSC Photos at Visit 02
5. Laboratory Analyses and Sample Letters	13. Participant Status
6. Activity Calendar	14. No Sunlight Exposure Questionnaire
7. Accrual Report	15. Visit Trend Report
8. Accrual by Age and Drusen Category	

### MATERIALS

1. Instructions for Taking the Trial Medication	5. Reminder for Followup Visit (Card)
2. Instructions for Taking the Study Medication	6. Participant Identification (Card)
3. Trial Medication Response Card	7. Diet Guidelines for Study Participants
4. Reminder for Next Visit (Card)	8. Return Requested Sample Letter

\* **Generated by the AREDS Interactive Data Entry System from data entered as follows:**

**Photograph Shipping Manifest:** Uses data entered into shipment database and prints to a hard copy.

**Ophthalmologist Confirmation:** Uses photograph grading data transmitted to the Coordinating Center from the Reading Center and prints a hard copy.

**Study Supplement Order form:** Uses data entered into the Supplement Order form and prints to a hard copy.

\*\* **Form will not be key-entered at the Clinical Center.**

\*\*\* **Form Utilized by appropriate coding/completion of Annual/Nonannual followup form.**

\*\*\*\* **System forms only.**

+ **WordPerfect Utility Document.**