

## Chapter 7

### EXAMINATION PROCEDURES

#### 7.1 INTRODUCTION

The procedures for carrying out the examinations required in the study are described in this chapter. Required ocular examinations include refraction and visual acuity measurements, intraocular pressure measurement, and ophthalmoscopic examination. General characteristic assessments include measurement of height, weight, and blood pressure and determination of past medical history. Risk factor assessments will require the administration of the food frequency and sunlight exposure questionnaires as well as collection of blood specimens. Procedures for participant identification, masking, distribution and management of the supplementation, adherence assessment, and home visit examination are also described. Procedures for taking photographs of the lens and fundus are described in detail in Chapter 8. The schedule and description of participant visits in Chapter 6 outline the examinations required during each visit.

#### 7.2 REFRACTION AND VISUAL ACUITY

A manifest refraction and visual acuity measurement according to the detailed study protocol must be performed during (a) the Qualifying Visit when the visual acuity score using Chart R is 73 letters or less in at least one eye, (b) the Randomization Visit, (c) Annual Visits, and (d) any Nonannual Visit when the visual acuity score using Chart R has dropped by 10 letters or more compared to the Randomization Visit score for the first time. Participants' pupils should not be dilated at the time of visual acuity testing at any study visit; except they may be dilated during the Qualifying Visit. Pinhole acuity will not be tested as part of AREDS. At the Qualifying Visit, visual acuity may be initially assessed utilizing the participant's current distance glasses. At the Nonannual Visits, visual acuity is initially assessed utilizing the previously obtained manifest refraction. Participants will be asked to read the letters on Chart R only (not Charts 1 or 2), using the equipment described in Section 7.2.1. They will start reading from the top left-most letters--first with the right eye and then with the left eye. A visual acuity score will be calculated as described in Section 7.2.3.3. If at the Qualifying Visit the visual acuity is 74 letters or more in each eye or if at a Nonannual Visit the visual acuity is within nine letters of the Randomization Visit score in each eye, or a vision drop has already been documented in each eye, the visual acuities measured will be entered on the study form. For these participants, a manifest refraction and measurement of best-corrected visual acuity, using the detailed protocol (Sections 7.2.1 - 7.2.3), will not be required.

##### 7.2.1 Visual Acuity Equipment and Facilities

7.2.1.1 Introduction. The visual acuity of participants will be measured according to the standard procedure developed for the Early Treatment diabetic Retinopathy Study (ETDRS) and adapted for AREDS. The procedure is described in this section. The following equipment is used

in AREDS: a set of three Lighthouse Distance Visual Acuity Test charts (second edition), which are modified ETDRS Charts 1, 2, and R,<sup>1</sup> and a retroilluminated box providing standardized chart illumination, as modified from the design by Ferris and Sperduto.<sup>2</sup> The charts and boxes are manufactured by:

Lighthouse Low Vision Products  
36-02 Northern Boulevard  
Long Island, New York 11101  
Telephone: (718) 937-6959.

Visual acuity testing in AREDS is required at a distance of 4 meters and, for participants with sufficiently reduced vision, at 1 meter. The 4-meter distance should be marked clearly and permanently; the 1-meter distance must be measured, with a 1-meter stick, with the participant in a chair (Section 7.2.1.5).

7.2.1.2 Visual acuity charts. Charts 1 and 2 are used for testing the right and left eye, respectively, and Chart R is used for refraction. The features of the charts are five high-contrast Sloan letters in each of 14 lines, lines of equal difficulty, and a geometric progression of letter size (and, thus, an arithmetic progression of the logarithm of minimum angle of resolution) from line to line. Charts 1, 2, and R have different letter sequences. Participants should be prevented from seeing Charts 1 and 2 until refraction has been completed and the visual acuity test begins.

7.2.1.3 Visual acuity box. The dimensions of the light box are 24 and 3/4 inches by 25 and 3/4 inches by 7 inches. The box can be mounted on a wall or on a cylindrical stand manufactured by Lighthouse Low Vision Products. The stand is mounted on a five-pronged wheel base, with each prong about 14 inches long; two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied.

The light box should be mounted at a height such that the top of the third row of letters (0.8 LogMAR) is  $49 \pm 2$  inches from the floor.

The rear of the box provides storage space for the two charts not being used.

7.2.1.4 Illumination. Most of the room lights should be turned off during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect. With the box light off, not more than 15 foot-candles of light should fall on the center of the chart.

The visual acuity light box is equipped with two General Electric Cool Daylight 20-watt fluorescent tubes and a ballast. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2,000 hours,

- ! New tubes should be kept "on" for about 4 days (96 hours, does not have to be continuous), and
- ! All tubes should be replaced once a year. Clinical Centers are encouraged to maintain schedules for tube replacement. Status of tubes will be checked manually at protocol review visits.

The fluorescent tubes should also be checked periodically for proper functioning. Replacement tubes can be purchased at a local store or from Lighthouse Low Vision Products.

Each tube is partly covered by a 14-inch fenestrated sleeve, open in the back, which serves as a baffle to reduce illumination. Each sleeve should be centered on the tube such that an equal length of tube (4 and 3/16 inches) is left uncovered to the right and left of the sleeve. The openings in the backs of the sleeves should be oriented to point directly toward the back of the box (ie, the sleeves should not be tilted up or down). Also, the lower sleeve has a cutout that should point down toward the ballast, although many boxes shipped since 1997 lack this feature.

7.2.1.5 4- and 1-meter visual acuity lanes. A distance of exactly 4 meters (13 feet and 1.5 inches, or 157.5 inches) is required between the participant's eyes and the visual acuity chart for the 4-meter test, and a distance of exactly 1 meter (39 and 3/8 inches) is required for the 1-meter test.

The room for visual acuity testing must have, in addition to the 4-meter lane, space for the visual acuity box (and possibly a stand) and space for the participant. Minimum room-length requirements vary according to how the box is mounted and whether the participant sits in a chair or stands for the 4-meter test.

- ! Wall-mounted box: In addition to the 4-meter lane, 7 inches must be allowed for the depth of the box plus space for the participant to sit or stand.
- ! Stand-mounted box: In addition to the 4-meter lane, 13 inches must be allowed for two of the stand's casters to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the participant to sit or stand.

### Marking the distance

#### 4 meters

1. If the chair and visual acuity box are permanently affixed, distance measurements need to be made only once and no floor marks are needed to ensure the correct distance.
2. If the box is mounted on the wall but the participant's chair is not permanently affixed, the 4-meter distance of the participant's eye from the chart must be marked clearly and permanently.
3. If the box is mounted on a movable stand, the 4-meter distance must be marked clearly and permanently on the floor. The location and orientation of the box must be rechecked each time a new chart is put in place or the box is touched. When the stand touches the rear wall of the room, two of the five casters should touch the wall.

## 1 meter

The 1-meter distance is measured from the eye of the participant, seated comfortably in a chair with his or her back firmly placed against the chair's back, to the center of the second or fourth letter of the third line of the chart. The stick can be homemade (eg, a dowel rod) or purchased at a local hardware store or by mail (eg, from Johnson Level and Tool Manufacturing Company, Inc., Mequon, Wisconsin).

### 7.2.2 Refraction Technique

7.2.2.1 Introduction. The technique described below is required for AREDS participants whenever a manifest refraction and best-corrected visual acuity measurement is indicated by the study protocol (Qualifying Visit, Annual Visits, and Randomization or Nonannual Visit at which a change in the visual acuity score of 10 or more letters is observed in either eye). Any standard visual acuity chart, such as Refraction Chart R or a Projecto-Chart, and any test distance can be used for determining the best lens correction in each eye. This is permitted so that any refraction room at the Clinical Center can be used, minimizing waiting time for the participant. If the standardized test (4-meters, Chart R) is not used, however, an over-refraction with spheres should be done with Chart R at 4 meters prior to testing visual acuity (Section 7.2.2.7, Adjustment for nonstandardized test conditions). Charts 1 and 2 are not used for refraction, only for visual acuity testing. The right eye is refracted first and then the left eye.

7.2.2.2 Beginning approximate refraction. If the participant wears contact lenses and has glasses, he or she should be told not to wear the contact lenses on the day of the examination. If the participant appears for the examination wearing contact lenses (because he or she has forgotten to follow the instructions or because he or she has no glasses), the contact lenses should be removed and refraction and visual acuity testing should not begin for at least half an hour.

The result of a subjective refraction on a previous visit can be used as the beginning approximate refraction. If this is not available, the procedures described below should be followed.

1. If the participant's uncorrected visual acuity is 20/200 or better and the participant does not have glasses for distance vision, the beginning approximate refraction is no lens correction (plano).
2. If the participant's uncorrected visual acuity is less than 20/200 in either eye with the participant's present distance glasses (or without correction, if the participant does not have glasses), retinoscopy should be performed by an examiner proficient in this procedure. An acceptable alternative is to conduct an arbitrary trial with any lenses to bring acuity to 20/200 or better; another is to use an automated refractor. The lens corrections obtained are used as the beginning approximate refraction for determining best-corrected visual acuity (Section 7.2.3).

3. If the participant's visual acuity is 20/200 or better with the participant's present distance glasses, the glasses are measured with a lensometer and these measurements are used as the beginning approximate refraction.

If the participant's visual acuity measures worse than 20/200 (less than 4 letters at 4 meters) due to decreased vision or an inability to cooperate, special refraction and visual acuity measurement procedures may be required for participants who have reduced visual acuity or difficulties in cooperating with the examination (see Section 7.2.2.7).

**7.2.2.3 Subjective refraction.** The trial frame is placed and adjusted on the participant's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. (It is permissible to use a Phoropter for subjective refraction. However, for testing visual acuity (Section 7.2.3), the lenses from the final Phoropter refraction must be placed in a trial frame and the final sphere must be rechecked as described in Section 7.2.2.6, **Refining final spherical power**). The left eye is occluded and the beginning approximate refraction, as determined above, is placed in the right lens cells with the cylindrical correction anterior. If AREDS Chart R is used, it should be read at a distance of 4 meters. Other standard eye charts may be read at a distance of 10 to 20 feet directly or with a mirror (if visual acuity is too poor for the participant to see the largest letters on the chart at this distance, Section 7.2.3.2, **1-meter test**).

**7.2.2.4 Determination of spherical refraction.** The visual acuity of the right eye is assessed and noted. A +0.50 sphere is then held in front of the right eye and the participant is asked if the vision is "better," "worse," or "no different" while he or she is looking at the smallest line read well.

1. If vision is improved or there is no change, the sphere in the trial frame is replaced with one that is one-half diopter more plus. The +0.50 sphere is held in front of the right eye again and the participant is asked again if the vision is "better," "worse," or "no different." This process of increasing the plus sphere in the trial frame is repeated until the participant says that the +0.50 sphere held in front of the trial frame makes the vision worse. When the participant responds that the vision is made "worse," the lens should be left in place for 10 to 15 seconds in an attempt to evaluate whether the participant is accommodating (an unlikely situation in a population over age 60). If the vision clears during this period, the +0.50 sphere may be added again and succeeding attempts to evaluate additional plus lenses should be accompanied with a 10- to 15-second delay. If there is no evidence of unrelaxed accommodation, the delay period while assessing plus lenses is not necessary at any time further in the examination.
2. Whenever the participant says that the vision is "worse" and remains worse, the +0.50 sphere is removed from in front of the trial frame.

By this process, the highest-plus or least-minus sphere that is tolerated without blurring the participant's vision is determined. After determining this highest-plus or least-minus sphere, the participant is asked to read the smallest line possible.

Next, a -0.37 sphere is held in front of the trial frame and the participant is asked if the vision is "better," "worse," or "no different."

1. If vision is improved, the participant is requested to read the chart and if at least one more letter is read, the sphere in the trial frame is replaced by a sphere that is 0.25 diopter less plus.

In certain situations, the participant is unable to read more letters, but is convinced that the vision is actually improved. If the examiner believes that this is the case, the additional minus lens can be added. At any stage in the examination, no more than 0.25 diopters of minus should be added without an increase in the number of letters read correctly. The additional minus lens should not be added if the participant reads fewer letters but states that acuity is better. There is a general attempt in this refraction protocol to avoid "over-minusing" the participants. However, when plus cylinders are in the refraction, one must be careful not to unnecessarily withhold minus which may be necessary for the participant to accept the needed plus cylinders later in the refraction. Minus spherical power is added in -0.25-diopter increments until the participant shows no further improvement in vision. If minus power is added, a +0.50 sphere is tried again to determine if more plus will be accepted.

2. If the participant says the vision is "not different" or "worse" no minus power should be added and the spherical determinations complete.

7.2.2.5 Determination of cylindrical refraction. For purposes of this discussion, only plus cylinder techniques are presented.

1. Cylinder axis determination. If the beginning approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by adding a 0.25, 0.37, or 0.50 diopter cross-cylinder, first with the positive axis 45 degrees to one side of the cylinder axis, and then with the positive axis 45 degrees to the opposite side of the cylinder axis. Since neither position may produce a clear image, the participant is encouraged to select the position producing "less blur" while fixing on a single round letter on the line above the lowest line on the chart he or she is able to read when the cross-cylinder is not held up before the trial frame. If the participant cannot choose between the two positions of the cross-cylinder at the beginning of this test, the axis of the cylinder is moved 5 to 15 degrees, first in one direction and then in the other, with the cross-cylinder being checked in each position to confirm that the original axis was indeed correct. If the participant prefers one position of the cross-cylinder to the other and the cylinder in the trial frame is plus, the axis of the cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder when it is in the position found to be less blurry by the participant.

(When the power of the cylinder is low or the participant's discrimination is poor, larger shifts will produce more clear-cut answers.) The cross-cylinder is tried again with the positive axis 45 degrees first to one side and then to the opposite side of the new cylinder axis to determine which position is producing less blur.

If the participant finds one position less blurry, the axis of the plus cylinder is moved toward the positive axis of the cross-cylinder. Testing for change of axis is repeated until the participant finds neither position definitely better than the other.

2. Cylinder power determination. Change in cylinder power is tested by adding the cross-cylinder, first with the positive axis and then with the negative axis coincident with the cylinder axis. For this test, the participant is requested to focus attention on a round letter on the lowest line on the chart he or she is able to read. If the participant prefers the positive axis coincident with the cylinder axis, the power of the correcting plus cylinder is increased by an additional +0.25 diopter. If the participant prefers the negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. The process is repeated until the participant finds neither position definitely better than the other. As plus cylinder is added, the examiner should recognize that the spherical equivalent of the refraction is being changed. More minus spheres may be needed as plus cylinders are added. When using plus cylinders for every 0.50 diopter of cylinder power added, the sphere should be changed by -0.25 diopter. If, at any time, the preference with the cross-cylinder indicates that cylinder power should be removed entirely, the 0.25 cylinder should be rotated 90 degrees from its original position. The axis should be refined and the power should be tested again.

If the beginning refraction is a "pure" sphere, the presence of astigmatism is tested by arbitrarily placing a +0.25 cylinder at 180 degrees in the trial frame, after having determined the highest-plus or least-minus sphere producing minimal blurring of vision, as described above. The refraction is then continued by using the cross-cylinder to test for cylinder axis and then cylinder power using the cross-cylinder technique outlined above. If, at any time, the preference with the cross-cylinder indicates that cylinder power should be removed entirely, the 0.25 cylinder should be rotated 90 degrees from its original position and the power should be tested again. At this point, if the participant prefers additional power, it should be added. If, on the other hand, the participant prefers to remove the +0.25, it should be removed and the final refraction is then purely spherical. An example of this procedure follows:

Beginning refraction: -2.50 + 0.25 axis 37 degrees. Use of the cross-cylinder to check cylinder axis indicates that the participant prefers the 37-degree axis. If, on using the cross-cylinder to check cylinder power, the participant wants the 0.25 cylinder removed, rotate the cylinder to 127 degrees and test for cylinder power again. If additional power is preferred, add it.

If the preference with the cylinder at 127 degrees is to remove the 0.25 cylinder, this should be done and the resulting refraction is -2.50.

Minus cylinders may be used instead of plus cylinders to determine the best correction for the cylinder power and axis. If minus cylinders are used, the above procedure must be revised to reflect the change in sign.

**7.2.2.6 Refining final spherical power.** When neither the power nor the axis of the cylinder can be improved, the power of the sphere is refined by testing with +0.25 sphere and -0.37 sphere and changing the spherical power as indicated in Section 7.2.2.4. If the sphere is changed at this point, the cylinder should be rechecked. This process is repeated until no further significant lens changes are made.

This refraction protocol can be summarized as follows. First, having eliminated any possible accommodation with plus spheres, the spherical equivalent power is placed on the retina. Then the cylinder power and cylinder axis are assessed. This process of checking sphere, cylinder axis, and cylinder power is repeated until there are no changes that result in an increased number of letters being read. Ideally, at the end of the refraction, the sphere is checked and the participant neither tolerates increased plus nor improves with increased minus spheres. Then the axis is checked and no change in axis is indicated. Finally, the cylindrical power is checked and no change in this is indicated. At this point, the refraction is completed. Sometimes this endpoint cannot be reached because there is an unending number of small corrections at each repetition of the process. When it becomes clear that these small changes are not resulting in an increased number of letters read correctly, the examiner can terminate the refraction.

The lens corrections obtained in this way for the right eye are recorded on the Visual Acuity Worksheet as the corrections obtained by subjective refraction for the right eye. The entire process is repeated for the left eye, and these lens corrections are also recorded on the Visual Acuity Worksheet as the corrections obtained by subjective refraction for the left eye.

**7.2.2.7 Adjustment for nonstandardized test conditions.** If a test distance other than 4 meters is used for refraction, the participant should be taken to the site of visual acuity testing (Section 7.2.1.5). At this site, a final adjustment of the sphere (as outlined in Section 7.2.2.6, Refining final spherical power) should be made at 4 meters just before visual acuity testing, using Refraction Chart R with appropriate lighting. If this refraction differs from the initial refraction, this lens correction should be recorded on the Visual Acuity Worksheets. Similarly, if a Phoropter is used for the subjective refraction, a final check on the sphere (as described in Section 7.2.2.6) should be performed with a trial frame using the 4-meter refraction lane and Refraction Chart R. A change of spherical power in these circumstances does not require rechecking the cylinder power or axis.

If it is not possible to perform a refraction at the 4-meter distance because of decreased vision or impaired mental aptitude, which prohibits the participant from correctly reading 4 or more letters, the refraction should be attempted at 1 meter. Before attempting the 1-meter refraction, +0.75 sphere must be added to the last 4-meter refraction obtained (during follow-up this is the previous refraction result obtained from the refraction data sheet), which is to be used as the starting refraction. If the subjective refraction can be successfully performed at 1 meter, a +0.75 sphere should be subtracted from the final 1-meter refraction to make the correction appropriate for the 4-meter distance. The refraction procedure at 1 meter is the same as the procedure for 4 meters. However, if the participant

is unable to discern changes in letter clarity using the lens increments outlined for the 4-meter refraction, larger increments of lens power should be used. When checking the sphere,  $\pm 1.00$  diopter should be tested. If the participant still cannot perceive any difference in clarity, changes up to  $\pm 3.00$  diopters can be attempted. Cylindrical refraction can be assessed with the 0.50 or 1.00 diopter Jackson cross-cylinder rather than the 0.25 diopter cross-cylinder. When changing the sphere power, use 1.00 diopter increments for adding plus, and 0.50 diopter increments for adding minus. When changing cylinder power, add or subtract cylinder power in 0.50 diopter increments.

If, at the end of the refraction process at 1 meter (still on Chart R), the participant is consistently reading letters on the eighth line or lower, he/she should be moved back to 4 meters, and the procedures for the 4-meter refraction should be followed (still on Chart R).

For participants who have had a decrease in mental ability and now find it difficult to provide reliable answers for the subjective refraction, modifications of the standard procedures may be necessary. The examiner can point at specific letters to assist the participant to concentrate. If the examination is still deemed unreliable, it may be necessary to use retinoscopy or auto-refraction to obtain the best possible refraction. During the visual acuity examination it may be necessary to point to specific letters and/or have the participant take rest breaks. If the final visual acuity obtained differs by 10 or more letters from Randomization, and is still thought to be totally unreliable, enter the score on the worksheet and code unreliable as the reason for vision loss on the Annual or Non-annual Followup Form.

As always, when testing final visual acuity the testing is started at 4 meters (on charts 1&2).

7.2.2.8 Refraction for participant with poor visual acuity. If it is not possible to perform a subjective refraction at 10 to 20 feet because visual acuity is too poor for the participant to see the largest letters on the refraction chart at this distance, the refraction should be attempted at 1 meter. If the subjective refraction can be performed successfully at 1 meter, a +0.75 sphere should be subtracted from the 1-meter refraction to make the correction appropriate for the 4-meter distance. This correction should be entered on the Visual Acuity Worksheet in the space provided for distance subjective refraction. (NOTE: Visual acuity will be tested first at the 4-meter distance even if the participant cannot be refracted at this distance. If the number of letters read correctly at 4 meters is 19 or less, visual acuity must also be tested at 1 meter, in which case the +0.75 sphere should be added to the 4-meter refraction.)

7.2.2.9 Special Situations. Occasionally one will need to perform refraction and visual acuity on patients with medical or other conditions that make the routine testing difficult, such as Alzheimer's Disease, after a stroke, or other problems that make strict adherence to the protocol difficult. In such cases one should attempt to follow the protocol as carefully as possible recognizing the special needs of the patient. For example, some patients are unable to concentrate long enough to read the entire chart from top to bottom. One might take a break after reading several lines. It may be necessary to point to letters to get the patient started at the appropriate line or to get them to read letters at all. The goal is to follow the protocol as closely as possible, recognizing that, on occasion, special circumstances may require some minor deviations to get the best estimate of the patient's true best corrected visual acuity.

### 7.2.3 Testing Best-Corrected Visual Acuity

7.2.3.1 4-meter test. **TESTING OF ALL EYES BEGINS AT 4 METERS.** First, the right eye is tested with Chart 1 and then the left eye is tested with Chart 2. Each chart should remain hidden from view until the eye in question is ready for testing.

The distance from the participant's eyes to the visual acuity chart must be exactly 4.0 meters (13 feet and 1.5 inches, or 157.5 inches). The participant may stand or sit for the 4-meter visual acuity test. If the participant is seated, his or her back should fit firmly touching the back of the chair. The examiner should ensure that the participant is standing or sitting comfortably, that the head does not move forward or backward during the test, and that the participant's eyes remain at the 4-meter distance.

The testing procedure for visual acuity is based on the principle that the objective is to test visual acuity and not intelligence or the ability to concentrate or follow or remember instructions (although all of these factors are involved). The participant should be told that the chart has letters only and no numbers. If the participant forgets this instruction and reads a number, he or she should be reminded that the chart contains no numbers and the examiner should request a letter in lieu of the number.

The participant should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter and to not proceed until the participant has given a definite response. It may be useful for the examiner to demonstrate the letter-a-second pace by reciting "A, B, C, . . ." If, at any point, the participant reads quickly, he or she should be asked to stop and read slowly. If the participant loses his or her place in reading or the examiner loses his or her place (possibly because the letters are read too quickly), the examiner should ask the participant to go back to where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test except for those situations as outlined in Section 7.2.2.7.

Each letter is scored as right or wrong (Section 7.2.3.3). Once a participant has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the participant changes a response aloud (eg, "That was a 'C', not an 'O'") before he or she has read aloud the next letter, then the change should be accepted. If the participant changes a response after beginning to read the next letter, the change is not accepted.

When the participant says he or she cannot read a letter, he or she should be encouraged to guess. If the participant identifies a letter as one of two or more letters, he or she should be asked to choose one letter and, if necessary, to guess even if the next letter has already been read. The examiner may suggest that the participant turn or shake his or her head in any manner if this improves visual acuity. If the participant does this, care must be taken to ensure that the fellow eye remains covered. When it becomes evident that no further meaningful readings can be made, despite urges to read or guess, the examiner should stop the test for that eye.

There are several reasons for encouraging participants to guess: (1) Participants' statements that they cannot identify a letter are often unreliable; (2) encouraging them to guess helps to

maximize the participant's effort; (3) it helps to assure uniformity among procedures performed in different clinics; and (4) it may help to prevent participant bias (malingering).

7.2.3.2 1-meter test. Eyes reading 19 or fewer letters correctly at 4 meters should be tested at 1 meter. If the trial frame is to be removed when changing the test distance from 4 meters to 1 meter, the testing chart (Chart 1 or 2) should first be removed from view to prevent the participant from reading the chart with the fellow eye.

Before testing at 1 meter, a +0.75 sphere should be added to the 4- meter correction already in the trial frame to compensate for the closer testing distance. The participant may stand or sit for the 4-meter test, but must sit for the 1-meter test. (As indicated in Sections 7.2.1.5 and 7.2.3.1, the participant should be seated comfortably with his or her back firmly placed against the back of the chair.) The avoidance of any head movement forward or backward is particularly important during the 1-meter test. The participant should be asked to read only the first six lines at 1 meter, making 30 the maximum score attainable at that distance (Section 7.2.3.3).

After the test of the right eye is completed, occlude the left eye and replace Chart 1 by Chart 2. The test is repeated for the left eye, starting at 4 meters. When testing of the left eye is completed, Chart 2 should be removed from view; Chart R may be mounted in preparation for the next participant.

7.2.3.3 Scoring best-corrected visual acuity. The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. Letters read incorrectly and letters for which no guesses are made are not marked on the form. Each letter read correctly is scored as one point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded on the Visual Acuity Worksheet after testing is completed. If testing at 1 meter is not required, 30 points are automatically scored for the 1-meter test. The total combined score (ie, the sum of the 4- and 1-meter scores) and the approximate Snellen fraction, which is determined based on the lowest line read with one or fewer mistakes, are recorded on the Visual Acuity Worksheet or the appropriate AREDS form.

Exhibit 7-1, taken from Ferris et al,<sup>1</sup> lists visual acuity in various units of measurement equivalent to the acuity represented by the expected number of letters identified correctly on Early Treatment Diabetic Retinopathy Study (ETDRS) or Lighthouse charts.

7.2.3.4 Light perception and no light perception. If visual acuity is so poor that the participant cannot read any of the largest letters at 1 meter (ie, the number of letters read correctly at 1 meter is zero), light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope light should be in focus at 3 feet with the rheostat set at maximum voltage. From a distance of 3 feet, the beam should be directed in and out of the eye at least four times, and the participant should be asked to respond when he or she sees the light. If the examiner is convinced that the participant perceives the light, vision should be recorded as "light perception"; if not, vision should be recorded as "no light perception."

7.2.3.5 Legal blindness. Assessing legal blindness (20/200 or worse) with the visual acuity charts used in this study may present a problem. On standard Snellen charts, the line below 20/200 is 20/100, and so the usual definition of legal blindness (20/200 or worse) could be reworded "worse

than 20/100." The AREDS charts, however, contain two lines of 20/160 and 20/125 between the 20/200 and 20/100 lines, and so a participant, who should be considered legally blind, may actually read better than 20/200 but worse than 20/100 when tested on the AREDS charts. This may prevent participants from being designated legally blind, depriving them of economic and social benefits. It is, therefore, suggested that legal blindness be assessed with standard Snellen acuity charts.

7.2.3.6 Scoring unreliable visual acuity. When examiners conclude that the final visual acuity score is totally unreliable due to the participant's decreased mental ability, the visual acuity score must still be entered on the Annual or Nonannual Visit form. If the score obtained differs by 10 or more letters from Randomization, and the examiner has ruled out other factors as a cause for the loss and is convinced the loss is due to unreliable testing, the reason for vision loss may be coded as "unreliable".

### 7.3 INTRAOCULAR PRESSURE

Intraocular pressure (IOP) should be measured using an applanation tonometer by personnel experienced in the procedure. A pneumatonometer may be used if an applanation tonometer is not available. Both eyes will be tested, with the test of the right eye preceding that of the left eye. The measurement must be made on an eye that has not received medications to dilate the pupil. 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 the 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.

#### 7.3.1 Applanation Tonometer Procedure

After topical anesthesia, a moistened fluorescein strip will be applied to the eye, or a combination fluorescein anesthetic may be used. A single measurement is made as follows: While the fellow eye fixes horizontally across the room, the examiner brings the tip of the instrument to the eye to be examined, adjusting the focus, shape, and centering of the mires with small movements of the tip. If the participant has astigmatism in excess of 3 diopters, the operator rotates the applanation prism until the red line corresponds to the orientation of the longer axis of the elliptical applanated area. The operator varies the applanating force on the cornea by turning the dial until the inner borders of the fluorescent mires barely touch at the midpoint of the pulse swing. The operator removes the tip from the cornea and records, on the Eligibility and Randomization or Nonannual Visit form, the reading on the dial rounded to the nearest integer. If, for example, the measurement indicated is less than 16.5, then 16 would be recorded as the measurement.

### 7.3.2 Pneumatonometer Procedures

Seat the participant comfortably for all IOP measurements. Be certain that a clean, aseptic, membrane is installed on the probe tip before attempting an IOP measurement. Membranes may be prepared for use by wiping them with a sterile gauze pad soaked in 70% isopropyl alcohol (membranes may also be immersed in a similar solution prior to use). Allow sufficient time for the alcohol to evaporate before contacting the participant's cornea. If the unit is equipped with the Modular Air Compressor, turn the compressor "ON". Gas flow is started or stopped by use of the foot pedal in those models equipped with a freon gas supply. Turn the main tonometer unit (MTU) "ON". The MTU display will read "Memory Check-OK" immediately after power-up, after which the MTU will read "Select Function". Select "IOP, OD".

Instill a drop of topical anesthetic in each eye. The use of a fluorescein strip or combination fluorescein/anesthetic drop is not necessary with this device. Have the participant fixate on a target that is situated approximately at the participant's eye level. Restrain the participant's lids, if necessary. One of the major contributors to variability and inaccuracy is excessive force applied to the eye through the lids in the attempt to restrain blinking. The upper lid should be held lightly against the orbital ridge by the thumb or first finger of the examiner's free hand. The examiner should be certain that he/she is in a position to see that the center of the sensor tip will be tangent to the participant's cornea at the point of contact (perpendicular to the participant's line of sight). Hold the sensor lightly between the thumb and index finger and rest the remaining fingers on the participant's cheek. Depress the foot switch to start the air flow. Reminding the participant to concentrate on the fixation target, move the sensor into position, raising the rear (tubing) end of the sensor until the piston extends forward toward the eye.

Move the sensor toward the eye, aligning it so that the center of the tip will make contact close to the corneal apex. There will be no reading if a part other than the center makes the principle contact. It is all right if the coupling sleeve behind the tip is not perfectly straight, but avoid extreme bending. When the tip touches the cornea, continue to move the sensor handle toward the eye until the white housing is even with the black line on the piston. DO NOT move the sensor toward the eye such that the red line on the piston is covered, otherwise an incorrect reading will result, as the piston will not float properly.

If these procedures have been correctly followed, the tonometer should begin to record the pressure, as indicated by an audible, steady tone from the MTU. The tone will change from high to low pitch to tell the examiner that the measurement is complete and accurate. The probe can then be removed from the eye and the IOP recorded (as indicated on the MTU display), on the Eligibility and Randomization or Non-annual Visit form, and the reading rounded to the nearest integer. If, for example, the reading indicated on the MTU is less than 16.5, then 16 is recorded on the form. If the reading indicated on the MTU is greater than 16.5, then 17 is recorded on the form. The examiner can now test the other eye by selecting "IOP, OS" on the MTU function panel.

## 7.4 PUPIL DILATION AND OPHTHALMOSCOPIC EXAMINATION

Photographs must be taken through a maximally dilated pupil (Chapter 8). It is recommended that 2 sets each of 2.5% Neo-synephrine and 1% Mydriacyl be instilled 2-5 minutes

apart. At each ocular examination, the ophthalmologist examines the fundus, with special attention given to the macula, using direct ophthalmoscopy and/or, slit-lamp biomicroscopy. Ocular photography should be performed prior to a contact lens examination, which will distort the ocular surface and impair the quality of photographs.

## **7.5 HEIGHT AND WEIGHT MEASUREMENT**

Clinic staff must use a beam balance scale to measure the height and weight. The procedures are set forth below.

### **7.5.1 Participant Preparation**

- ! Explain the measurements to be taken.
- ! Ask the participant to remove his or her excess clothing; weight should be recorded with indoor clothing only.
- ! Ask the participant to remove her or her shoes.
- ! Check to see that the scale balance arm is set at "zero"; ie, that the sliding weight balances are set at "zero" and the scale indicator is centered.
- ! Ask the participant to step onto the platform of the scale, facing away from the scale.
- ! Instruct the participant to "stand up straight and tall; keep your back straight and hands relaxed and at your side, and your eyes looking straight ahead."
- ! Review the participant's position.

### **7.5.2 Height Measurement**

- ! Move height lever into place, touching crown of head (check with your hands).
- ! Carefully read measurement to nearest inch.
- ! Say measurement aloud.
- ! Record measurement in inches on the form.
- ! Lift lever from atop participant's head.
- ! Proceed to take weight measurement.

### 7.5.3 Weight Measurement

- ! Stand at back of scale.
- ! Slide bottom weight balance (100 lb) first to participant's estimated gross weight; make sure that the weight balance is locked into its slotted position.
- ! Slide the top arm weight balance into position so that the scale indicator is centered.
- ! Carefully read measurement to the nearest 1 lb (tick mark).
- ! Say measurement aloud.
- ! Record measurement in pounds (lb) on form, filling in any leading zero.
- ! Ask participant to step down and recover his or her shoes and any clothes.

## 7.6 BLOOD PRESSURE MEASUREMENT

Blood pressure measurements will be taken by a certified examiner using a standard mercury sphygmomanometer. Instructions for preparing the participant, using the proper techniques, utilizing equipment, and measuring and recording the blood pressure are provided below. Some institutions have installed electronic automated sphygmomanometers. In the interest of data consistency, standard mercury units are the instruments of choice; however it is recognized that staff at those centers may have no alternative.

### 7.6.1 Participant Preparation

1. The participant should be seated with feet flat and on the floor and legs uncrossed, with the right arm bared, supported, and positioned at heart level and should not have smoked, eaten, ingested caffeine or been exposed to exertion or cold for at least 30 minutes prior to the measurement. The participant should be seated and quiet for at least 5 minutes prior to the measurement, and requested not to talk while blood pressure is being taken.
2. Choose appropriate cuff size for arm to be tested. The rubber bladder should encircle at least two-thirds of the arm. If the cuff is too narrow, the blood pressure reading will be erroneously high; if it is too wide, the reading may be low. A cuff that is 12-14 cm wide is satisfactory for the average adult arm.

### 7.6.2 Technique

1. Use a standard mercury sphygmomanometer to measure the blood pressure. The mercury manometer must be handled carefully to avoid loss of mercury. The level of mercury in the tube should be observed with no pressure applied

to the cuff. If necessary, mercury should be added to the reservoir to bring the edge of the mercury meniscus exactly to the zero mark. The column of the usual desk or wall manometer must be vertical for correct reading. Some mobile or floor-based mercury manometers are designed to be read at a reclined angle and the gradations are adjusted accordingly. It is important that the instrument be used with the tube and its scale in the correct position. The tube of the mercury manometer should be inspected regularly for dirt or sign of oxidation. Clogging in the air vent or filter at the top of the manometer tube will cause the mercury column to respond sluggishly to declining pressure in the bladder and will cause an erroneous reading. The filter and the vent should be serviced at least annually to ensure continued accuracy.

2. Place lower edge of cuff with its tubing connections approximately 1 inch above natural crease of the inner aspect of elbow (2.5 cm above antecubital space).
3. Wrap cuff snugly about arm with inflatable inner bladder centered over area of brachial artery (medial surface of arm).
4. Be sure that the connecting tube attached to the mercury column is away from the participant's body and that the tube attached to the inflating bulb is close to the participant's body. Secure the wrapped cuff firmly by applying pressure on the locking fabric fastener over the area where it is applied to the cuff.
5. Attach the cuff connection and inflate the cuff while palpating the radial pulse and watching the mercury column. Begin to inflate the cuff until sufficient pressure is applied, at which point the pulse will no longer be felt. Deflate slowly at 2 mm per second until the pulse is felt again. Remember that number and immediately release all pressure in the cuff.
6. Add 30 mm Hg to the value at which the pulse was no longer felt. This value is the peak inflation level to which the cuff is to be inflated for all readings.

### 7.6.3 Stethoscope

1. The stethoscope should be a standard variety and in good condition. The stethoscope may be equipped with a bell endpiece or a diaphragm; some may have both. An examiner skilled in measuring blood pressure may find the diaphragm endpiece easier to use insofar as it is easier to hold with the fingers of one hand and covers a larger area. Some examiners will prefer the bell endpiece because it gives better sound reproduction.
2. Stethoscope ear tips should fit comfortably (but snugly) and block out most external noise.

#### 7.6.4 Measuring the Blood Pressure

1. Place the earpiece of the stethoscope into your ears.
2. Apply the endpiece of the stethoscope over the brachial artery, just below, but not touching, the cuff or tubing.
3. By closing the bulb thumb valve and squeezing the bulb, inflate the cuff at a rapid but smooth, continuous rate to the peak inflation level previously determined (Section 7.6.2, Step 6). The examiner's eyes should be level with the mid-range of the manometer scale and focused at the peak inflation level.
4. By operating the thumb valve slightly and maintaining a constant rate of deflation at approximately 2 to 3 mmHg per second, allow the cuff to deflate. As the pressure falls, the Korotkoff sounds become audible over the artery below the cuff and pass through the four phases as the pressure declines and sounds disappear. The muffling and disappearance are sometimes referred to as the 4th and 5th "points."
5. The five phases of Korotkoff sounds are as follows:
  - Phase 1 - The period marked by the first appearance of faint, clear "tapping" sounds that gradually increase in intensity.
  - Phase 2 - The period during which a murmur or "swishing" quality is heard.
  - Phase 3 - The period during which sounds are crisper and increase in intensity.
  - Phase 4 - The period marked by the distinct, abrupt muffling of sounds so that a soft, "blowing" quality is heard.
  - Phase 5 - The point at which sounds disappear.
6. The systolic blood pressure is marked by the point at which the initial "tapping" sound is heard (Phase I). To make certain the sound is not extraneous, one should hear two consecutive beats as the pressure falls. When the palpatory systolic pressure is higher, it should be recorded and noted as systolic pressure.
7. "Muffling" occurs when the crisp Korotkoff sounds change (recognized by a sudden diminution or disappearance of sound). This is the fourth phase. The fifth phase, when sounds become inaudible, is regarded as the best index of diastolic blood pressure in adults; this phase will be used for measuring diastolic blood pressure in AREDS. The accuracy of determining the fifth phase depends on the efficiency of the stethoscope and the auditory acuity of

the examiner. In some individuals, particularly hypertensive patients, the usual sounds heard over the brachial artery when the cuff pressure is high, disappear as the pressure is reduced and then reappear at a lower level. This early, temporary disappearance of sound is called the "auscultatory gap" and occurs during the latter part of phase 1 and phase 2. Because this gap may cover a range of 40 mmHg, one can seriously underestimate the systolic pressure or overestimate the diastolic pressure, unless its presence is excluded by first palpating the radial pulse until it disappears as the cuff pressure is raised.

8. The examiner should listen throughout the entire range of deflation until 10 mmHg below the level of the diastolic reading.
9. When all sounds have disappeared, the cuff may be fully deflated by opening the thumb valve, and the stethoscope earpiece may be removed from the ears.

#### 7.6.5 Recording the Blood Pressure

1. All readings should be made to the next even digit. For example, if the mercury is slightly above 82 mmHg, the reading should be recorded as 82 mmHg. Any reading (systolic or diastolic) that appears to fall exactly between markings on the column should be read to the next marking immediately above. All readings should be made at the top of the meniscus.
2. Record both systolic and diastolic pressures. The disappearance of Korotkoff sound (phase 5) should be used for diastolic reading.
3. Two readings will be taken and recorded on the Baseline Interview form (Appendix C). The first reading will be taken after the initiation of the baseline interview and the second near the end of the baseline interview. Each measurement should be taken on the same arm.

## 7.7 NUTRITION COMPONENT

### 7.7.1 Food Frequency Questionnaire

Specific instructions and guidelines for helping participants self-administer the food frequency questionnaire are provided in the Data Management Handbook. A summary description of the Food Frequency Questionnaire to be used in AREDS is provided below. See Appendix E for a full description of the development, context, and nutritional analysis of the AREDS Food Frequency Questionnaire.

7.7.1.1 Rationale. AREDS will assess the relationship between diet, particularly the intake of antioxidant nutrients, and the development of cataract or macular degeneration. The food frequency method (FF) was selected and nutritional analysis to measure the diet/disease association

in all study subjects rather than the 24-hour recall or food-record methods. The 24-hour recall and food-record methods are prospective methods that provide dietary information over a short time period. Multiple administrations of the 24-hour recall or food-record would be required to provide an estimate of usual intake and would require excessive respondent time and commitment. The FF method provides an estimate of an individual's usual food intake and, in AREDS, will focus on average intake over the past 1 year. The 24-hour recall method will be used in a sample of AREDS subjects to facilitate interpretation of data collected by the FF. (See Section 7.7.2 below).

The Block FF Questionnaire (FFQ)<sup>3</sup> was selected for use in AREDS because its reliability and validity have been assessed, and it has been used in several large epidemiologic studies of the eye. Results from AREDS may thus be compared with dietary data collected in other studies.

**7.7.1.2 The Block FFQ.** The full Block questionnaire includes 100 food items, plus additional questions on consumption of restaurant food, types of fats used in cooking, and vitamin and mineral use. The food list was developed on the basis of dietary intake data from the Second National Health and Nutrition Examination Survey (NHANES II).<sup>4-6</sup> Foods were included on the FF list if they contributed substantially to energy intake as well as intake of each of the 17 nutrients in the NHANES II database (calories, fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, protein, carbohydrate, vitamin A, vitamin C, calcium, iron, thiamin, riboflavin, phosphorus, potassium, and sodium). In constructing the food list, usual consumption and portion size of the food was considered. Zinc values are being added to the database, although the analytic methods available for zinc determination in some types of foods are not very reliable. Selenium nutrient values are not currently available in the database.

**7.7.1.3 Objectives.** Dietary data derived from the FFQ will provide a ranking of individuals by relative levels of nutrient intake. This relative ranking, by tertiles and quintiles, will enable investigators to evaluate hypotheses on the relationship between dietary intake of specific nutrients and development and progression of disease.

**7.7.1.4 Validity of the Block FFQ.** The correlation between specific nutrients derived from the FFQ and nutrients derived from a food record (the "gold standard") provides a measure of validity. Most correlations for micronutrients, excluding supplements, range from  $r = 0.5$  to  $r = 0.6$ . Vitamins A and E from the FFQ have the lowest correlations with values from the 24-hour recall and food-record methods but this more than likely reflects limitations of the food record than of the FFQ.

**7.7.1.5 Description of the FFQ.** The FFQ is designed as a self-administered questionnaire and takes approximately 45 minutes to complete. The 100 item FFQ was selected over the 60 item short-form questionnaire because it will provide better estimates of absolute values of calories and macronutrients in this elderly population with variable diets. Detailed instructions for administration are provided in the Data Management Handbook.

**7.7.1.6 Quality control.** If time permits, participants should complete the entire FFQ at the clinic. However if scheduling problems arise, each participant may begin the FFQ at the clinic by filling out at least the first four pages and completing the remainder at home. The completed portion of the FFQ will be reviewed by the Clinic Coordinator to assure completeness and consistency of responses. Any questions arising from this review will be verified with the participant.

Participants demonstrating an understanding of the requirements may complete the remainder of the questionnaire at home and return it at the Randomization Visit. Participants who fail to return the questionnaire must complete it prior to randomization. Forms will be machine-readable (a scanning machine will read them), so that key entry is not required.

7.7.1.7 Timing of Administration. The FFQ will be self-administered during the Qualifying Visit or the Randomization Visit. The FFQ will be administered to all participants at a followup visit. These data will provide an estimate of dietary change.

## 7.7.2 24-Hour Dietary Recall Study

7.7.2.1 Background and rationale. Public recommendations based on trial results will require information on the nutritional status of the AREDS study population. Should the trial results suggest the efficacy of high-dose supplementation, the nutritional status of the AREDS study population will be important in describing what population will likely benefit from supplementation. Alternatively, if the trial does not suggest efficacy of high-dose supplementation, questions about the nutritional status of the population will also arise. For instance, the supplements might be efficacious in a poorly-nourished group but not so in a well-nourished group that perhaps has reached a certain nutrient threshold above which additional supplementation is inconsequential.

As discussed in Section 7.7.1 (above) the FFQ provides a fairly robust estimate of usual dietary intake over the past year. The type of classification allowed by the FFQ, into high and low dietary exposure groups, generally results in energy-adjusted correlation coefficients correlating rankings obtained by the food frequency method with those by dietary diary records or recalls in the range of 0.3 to 0.7. The 24-hour dietary recall data on a sample of AREDS participants will allow evaluation of the stability of the rankings by nutrient intake as assessed by the FFQ. However, the FFQ does not provide point estimates of actual nutrient intake. The 24-hour dietary recalls on a sample of participants will provide point estimates of actual nutrient intake for a sample of the AREDS population. Obtaining two 24-hour dietary recalls for each sampled participant during a one-year period will reduce the seasonal variation in dietary reporting (two interviews six months apart will provide for dietary coverage of different seasonal food intakes), provide coverage of a one-year period corresponding to that of the FFQ, and reduce the intraindividual variability generally present in dietary assessment methods.

### 7.7.2.2 Objectives.

Primary objectives. The 24-hour dietary recall will be used to:

- a. Describe current dietary intake in a sample of AREDS participants.
- b. Estimate the proportion of AREDS participants at risk for low nutritional status.

Secondary objectives.

- a. Estimate the proportion of participants classified in the same quintile by nutrient intake obtained from the 24-hour dietary recall, food frequency, and biochemical measures methods.
- b. Describe the current nutritional status of a sample of AREDS participants using both the 24-hour recall and biochemical measures.

7.7.2.3. Methods. The data collection instrument to be used in this study is the 24-hour dietary recall (Telephone Recall). Recall interviews will be administered by one or more interviewers at the Nutrition Coordinating Center (NCC) at the University of Minnesota, which is under contract with the AREDS Coordinating Center. See Appendix E for the telephone script.

Population. The population to be studied for the 24-hour recall will be all participants from three of the AREDS clinics participating in the biochemical analysis component of the study. The chief advantage of studying this population is that the dietary data can be compared with serum levels of nutrients.

Sampling. From the three clinics combined, the Coordinating Center will select, by random sampling stratified by AMD Category, a total of 200 participants. From each of the four AMD Categories, 50 participants will be sampled. The Coordinating Center will also randomly select, from each AMD Category, an additional 10 participants who may be needed if initially selected participants decline to enter this protocol. Selection of a participant for the 24-hour recall will be indicated on the Pending Randomization Report. During the Randomization Visit, each selected participant will be asked by the Clinic Coordinator to take part in the 24-hour dietary recall to be administered at a later time. If the participant agrees to take part, informed consent will be obtained and a copy of the Participant's Schedule for Telephone Recall form will be completed (See Appendix B for a sample consent). The Clinic Coordinator will forward a copy of the Participant's Schedule for Telephone Recall, together with any other information needed to contact the participant, directly to the Nutrition Coordinating Center. The participant will also be given a copy of the Serving Portions Sheet. A notification of participation will be sent to the database administrator at the AREDS Coordinating Center, who will enter the registration number of the participant into a log.

The Participant's Schedule for Telephone Recall will be kept on file at the Nutrition Coordinating Center, with a copy provided to the interviewer. If the person declines to participate, the Clinic Coordinator will approach the next eligible (i.e., not already enrolled in the 24-hour recall component) AREDS participant indicated on the Pending Randomization Report.

Data collection. Provided with a listing of names and telephone numbers, the Nutrition Coordinating Center will contact participants within two weeks to conduct the recall interview, using the Participant's Schedule for Telephone Recall to maximize the probability of making contact at a time convenient to participants. The interviewer will enter all dietary intake information into the Minnesota Nutrition Data System. Upon completion of the Telephone Recall, the interviewer will review with the participant the entire interview and follow up on all missing foods required to complete the recall. If any further information is required from the participant, the interviewer will attempt to call back the same day to resolve the problem.

Approximately six months after the initial interview, the Nutrition Coordinating Center will conduct a second 24-hour recall interview with the participant.

Data management. Each interviewer will backup all recall data on a weekly basis. The Nutrition Coordinating Center will maintain a complete set of such backup records for the entire study. On a monthly basis, the Nutrition Coordinating Center will prepare and send to the Coordinating Center a diskette containing all recall data collected during that month. At the conclusion of the study, the Nutrition Coordinating Center will prepare a diskette containing the nutrient intake values for each participant in the study. All information forwarded to the Coordinating Center will be identified by registration number only. All participant names will be removed by the Nutrition Coordinating Center prior to forwarding data to the Coordinating Center.

#### 7.7.2.4 Statistical considerations.

Sample size. The sample size of 50 AREDS participants in each AMD Category and 200 participant in toto was developed on the basis of the resources available for the study. Exhibit 7-2 provides estimated standard deviations and 95-percent confidence interval widths for selected nutrients. For example, for dietary vitamin E, the 95-percent confidence interval width is 0.22 for a sample of 50 persons and 0.12 for 200 persons. The data for vitamin C in Exhibit 7-2 are at least 13 years old. Since vitamin C consumption in the United States may have changed in the intervening period, caution should be exercised in interpreting these data.

Analysis plan. The analyses will characterize the distribution of the averaged 24-hour recall estimates of nutrient intake from the two interviews for both macronutrients and micronutrients. Specifically, the mean, standard deviation, skewness, and kurtosis for each macro- and micronutrient will be calculated. Graphical frequencies will be plotted to determine if the nutrient values can be described by any of the known statistical frequency distributions (normal, log-normal, Poisson, etc). These characterizations will be performed for all participants and for participants by AMD Category, Clinical Center, and treatment assignment. Dietary intake of specific nutrients for the group will be compared to RDA levels.

Analyses related to the first of the secondary objectives of the study, ie, to estimate the degree of quintile agreement between 24-hour recall results, the FFQ, and the biochemical measures of nutritional status, will focus on the percent agreement in relative ranking between all pairs of the three methods; the kappa statistic summarizing the degree of concordance will also be calculated, as will rank correlation coefficients, as appropriate.

## 7.8 **SUNLIGHT EXPOSURE QUESTIONNAIRE**

As part of a followup visit, participants will be asked to provide information about their exposure to ultraviolet (UV) light, which has been suggested as a risk factor for cataract. UV exposure is greater closer to the equator and at higher elevations. In addition, a person may be protected from UV exposure by wearing a hat with a brim or bill, sunglasses, prescription glasses, or contact lenses. The questionnaire includes questions about the duration and location of outdoor

jobs or activities and the types of head and eye protection worn. These data will be used to estimate an individual's lifetime exposure to sunlight.

## 7.9 BLOOD SPECIMENS

All AREDS Clinical Centers, using local facilities for processing, will participate in baseline (at either Qualifying or Randomization Visit) and annual measurement of hematocrit levels. Three Clinical Centers and the NEI Clinical Center will collect additional blood samples for all participants prior to their initiation of study medication. Two Clinical Centers and the NEI Clinical Center will continue to collect additional blood samples at Annual Visits. These samples will be sent to the Central Laboratory for measuring levels of HDL/LDL, vitamins A, E, C, and beta-carotene and zinc. Procedures for collecting blood for the Central Laboratory are outlined in Chapter 18. All Clinical Centers will request consent from participants to draw blood for preparation of an immortalized cell line to be used for generic ancillary studies of AMD and cataract.

A participant's hematocrit (packed cell volume) is measured by the Clinical Center's local laboratory at the Qualifying Visit but may be measured at the Randomization Visit if the sample cannot be obtained at the Qualifying Visit. Hematocrit is also measured at all Annual Visits. If blood is not obtainable at the Annual Visit, it may be collected at the next Nonannual Visit. If the Annual Visit is missed, the sample may be obtained at the next Nonannual Visit. Blood collected in a capillary tube from a finger stick (skin puncture) is not acceptable. A hematocrit measured for AREDS may be performed at the local laboratory directly by centrifugation using macro or micromethods. If supplies are not available to perform one of the direct methods, an indirect automated method is acceptable. A brief description of each method for measuring hematocrit is provided below.

### 7.9.1 Macromethod (Wintrobe)

Using a Pasteur pipette, the Wintrobe tube is filled with blood from a completely filled purple-top EDTA anticoagulated Vacutainer tube. The hematocrit, expressed in percent, is calculated by dividing the height (in millimeters) of the red cell column in the Wintrobe tube (not including the buffy coat) after centrifugation, by the height (in millimeters) of the total specimen in the Wintrobe tube (red cell column, buffy coat and plasma) recorded prior to centrifugation.

### 7.9.2 Micromethod

A 7-cm capillary tube is filled by capillary attraction to 5 cm with blood from a completely filled purple-top EDTA anticoagulated Vacutainer tube. The hematocrit, expressed in percent, is calculated after centrifugation by dividing the length of the red cell column in the capillary tube (not including the buffy coat) by the length of the total specimen in the capillary tube (red cell column, buffy coat and plasma). Because the capillary tubes are not graduated, the length of the red cell column and the length of the total specimen must be measured separately using a magnifying glass and a ruler marked in millimeters or a commercially available measuring device.

### 7.9.3 Automated Method

In automated instruments the hematocrit is usually the product of the MCV (mean corpuscular volume) multiplied by the red blood cell count. Depending on the instrument used, the hematocrit is calculated at the same time the red blood cell count, hemoglobin and/or indices are performed.

### 7.9.4 Reporting

Results of hematocrit testing will be recorded on the Baseline and Annual Visit forms. If the local laboratory's turn-around time for blood work is fast ( $\leq 24$  hours), data entry of the completed Baseline or Annual Visit forms may be delayed to allow entry of the hematocrit. Alternatively, the database can be modified with the hematocrit result at a later date. The hematocrit, along with the method used to measure it, is recorded in the appropriate data field on the hard copy of the form and a copy of the lab report is retained in the participant's AREDS chart.

Each Clinical Center will be provided with the ability to generate a report detailing the results of laboratory work. For Clinical Centers participating in additional blood drawing these results will include cholesterol and hematocrit measurements. For Clinical Centers not participating in the additional blood drawing, only hematocrit results will be included. Clinical Centers will be notified by the Coordinating Center twice a month of any participant with an observed value in the alert range. The treating ophthalmologist must make the participant aware of results in the alert range and suggest followup procedures. If the results are not in the alert range, the Clinical Center may distribute the results according to its own Institutional Review Board policies. The Clinical Center may:

- ! Give the report to the participant at the next scheduled visit
- ! Mail it to the participant and the participant's personal physician
- ! Mail it to the participant only

Alert ranges are:

|                   | <u>Men</u>                           | <u>Women</u> |
|-------------------|--------------------------------------|--------------|
| Hematocrit        | outside Clinical Center normal range |              |
| Total Cholesterol | >280 mg/dL                           | >300 mg/dL   |

## 7.10 PARTICIPANT IDENTIFICATION AND DATE OF ENTRY

### 7.10.1 Participant Registration Number

A permanent, unique five-digit AREDS registration number is assigned to each participant in Phase I. The first two digits identify the center (51, 52, etc) and the last three digits are assigned

in order of sequential registration (001, 002, etc). Phase I participants who are eligible for Phase II will maintain their Phase I registration number in Phase II. Participants newly identified during Phase II will be assigned the next registration number in the sequence.

#### 7.10.2 Participant Name Code

In addition to the identification number, each participant is assigned a 6-letter name code, consisting of the first three letters of the participant's last name, the first two letters of the first name, and the middle initial. For example, the name code for John S. Doe is DOEJOS. Participants without middle names or initials receive an "X" as the sixth letter. The name code is retained even if the name changes.

The identification number and the name code are the only identifiers entered on the examination forms transmitted to the Coordinating Center. Together, they enable Coordinating Center staff to link all data records for a participant. It is therefore essential that these elements of information are recorded clearly, correctly, and consistently on all forms and materials used in the study.

#### 7.10.3 Date of Entry

A participant's official date of entry into Phase II of AREDS, or date of randomization, is the date of assignment of a bottle number.

### 7.11 MASKING

AREDS is a double-masked study. Both the examiner and the participant will be masked as to the treatment with dietary supplements. The antioxidants, zinc, and placebo are alike in appearance, smell, and taste. The dietary supplements used in the study will be distributed by the Drug Distribution Center (Chapter 17). They will be enclosed in bottles such that participants and clinic personnel will be unable to break the code, although the Drug Distribution Center can easily do so. The Coordinating Center will store the master list of bottle numbers so that, in an emergency, the Study Chairman may call the Coordinating Center to request unmasking. The Coordinating Center will refer the request to the Operations Committee for review and approval with prompt turnaround. The Clinic Director will also be supplied with sealed envelopes containing the codes to be opened only in an emergency when the Coordinating Center can not be reached (Section 7.15). All envelopes must be stored in a secure, locked file cabinet or drawer during the study, and will be collected at the end of the study.

## 7.12 STUDY INTERVENTION AND CENTRUM® ORDERING, DISTRIBUTION, AND STORAGE

### 7.12.1 Study Intervention and Centrum® Ordering

The Drug Distribution Center will provide each Clinical Center with a full supply of run-in supplements (Trial Medication), and a one-year supply of study supplements (Study Medication) and Centrum®. Clinical Centers may reorder study tablets and Centrum® using the AREDS Supplement Order form (Appendix C) not more than once every three months, but should reorder with enough frequency so that at a sufficient supply of tablets is available to supply participants scheduled to come to the clinic in the next month. The turn around time between medication ordering and receipt is approximately 10 days. A copy of the order form should be maintained in the clinic file.

When the shipment is received, the shipment must be verified by:

- (1) Checking the bottles received against the bottles ordered,
- (2) The supplement order screen in the AREDS Interactive Data Entry System will ask for the date the shipment was received and for verification that the shipment was correct. If correct, the Supplement Order shipment record is closed. If not correct, the number of bottles received must be key entered and discrepancies between amount ordered and amount received documented.

7.12.1.1 Run-in supplements (Trial Medication). Each Clinical Center will be provided with 25-26 boxes each containing 50 bottles of 56 tablets per bottle of placebo tablets (Trial Medication). This supply will be adequate to provide run-in supplement for all participants qualified. Each Clinical Center is expected to require no more than 25-26 boxes of Trial Medication to meet the needs of AREDS.

7.12.1.2 Centrum®. During the first six months and again during the second six months of Phase II each Clinical Center will initially be provided with 6 boxes of Centrum® (72 bottles per box each bottle containing 100 Centrum® tablets). This initial quantity will provide 200 participants with a 12-month supply of Centrum® for daily intake.

7.12.1.3 Study medication. During the first six months and again during the second 6 months of Phase II, each Clinical Center will be provided with 50 boxes each containing 50 bottles of 92 tablets per bottle of study tablets. Each box will include medication for only 1 bottle number (01-50). Each shipment will provide a 6-month supply of medication for 300 participants.

### 7.12.2 Dispensing of Study Medication

7.12.2.1 Run-in period (prerandomization). Participants will be given a 1-month supply of Trial Medication to take during the run-in period (between the Qualifying Visit and the Randomization Visit). The medication will be packaged in 2 bottles, each containing 56 tablets (labeled Trial Medication: Week 1--Week 4). Participants will be instructed to take 2 tablets in the morning with food and 2 tablets in the evening with food. The bottle must be brought back to the

clinic when the participant returns for the Eligibility and Randomization Visit, at which time the number of tablets remaining will be estimated and the participant's ability to adhere to taking medication on a daily basis assessed. In addition, participants supplementing with a multivitamin with or without minerals who wish to continue supplementation will be asked to stop taking their own supplement and take Centrum<sup>®</sup> instead during this run-in period. One or two bottles of Centrum<sup>®</sup> containing 100 tablets each will be provided to participants wishing to continue taking a multivitamin and mineral tablet during the run-in period. Two bottles of Centrum<sup>®</sup> should be provided if a participant is scheduled for the Randomization Visit more than 3 months after the Qualifying Visit.

7.12.2.2 Postrandomization. Following randomization and at each study visit, participants will be given enough bottles to provide sufficient numbers of tablets to take until the next clinic visit. All bottles dispensed should be placed in the AREDS tote box and the tote box placed in the AREDS medication bag. Each bottle contains 92 tablets of the assigned study supplement, labelled Study Medication. If the participant wishes to take a multivitamin and mineral tablet, 2 bottles of Centrum<sup>®</sup> containing 100 tablets each, will be supplied. The participant will be instructed to take two of the study tablets in the morning with food and two of the study tablets in the evening with food. If the participant is also taking Centrum<sup>®</sup>, it may be taken at any time during the day. Participants will be reminded not to take other "non-study" multivitamins with or without minerals or extra supplements containing nutrients used in AREDS and will be instructed to use the tote box and medication bag to return all bottles of study tablets at their next clinic visit regardless of whether they are full, partially full, or empty. The participant's adherence to taking the medication as prescribed will be assessed during each visit by completing a Supplementation Record and Adherence Worksheet. This form will also be used to track supplement distribution and study intervention inventory.

Supplements may be dispensed between visits if the participant is expected to run out of medication prior to the next visit or if he or she has lost the AREDS supplement. Anytime supplements are dispensed, a Supplementation Record and Adherence Worksheet must be completed.

### 7.12.3 Medication Storage

Adequate locked storage facilities must be available in each Clinical Center to hold approximately 80 boxes of Trial Medication and study tablets and 6 boxes of Centrum<sup>®</sup>. The total area required is approximately 70 cubic feet.

7.12.3.1 Run-in and study medication. The dimensions of the boxes containing the Trial Medication and Study Medication to be shipped by the Drug Distribution Center to each Clinical Center are:

1 foot x 4.5 inches x 23 inches.

Each box weighs about 12 pounds.

7.12.3.2 Centrum<sup>®</sup>. The dimensions of the boxes containing Centrum<sup>®</sup> are:

17 1/2 inches x 8 1/2 inches x 8 inches.

Each box weighs about 29 pounds.

## **7.13 ADHERENCE**

Participant adherence with the intervention will be monitored by an estimated tablet count. All bottles of medication (empty or full) are to be returned to the Clinical Center at every scheduled visit. An estimate of the number of tablets remaining will be recorded on the Supplementation Record and Adherence Worksheet. The AREDS Interactive Data Entry System will compute a adherence assessment when the worksheet is key-entered into the computer. Clinic Coordinators should discuss the importance of adherence with participants during each visit and encourage the participants to continue taking the intervention as prescribed.

## **7.14 REPORTING OF ADVERSE EXPERIENCES**

### **7.14.1 Adverse Experience Definitions**

An adverse experience is some unplanned, unwanted event which occurs to a person and which may or may not appear to be related to the use of study medication. While some events may not appear to be associated with the use of the study medication, a relationship may not become apparent until a number of reports accumulate from various Clinical Centers.

Adverse Experience. Any adverse reaction, toxicity, event, abnormal laboratory result, or effect which may possibly be associated with use of study medication.

Serious adverse experience. The FDA usually defines a serious adverse experience as one which is fatal, life-threatening, permanently disabling, requires prolonged hospitalization, is thought to have caused a congenital anomaly or cancer, or an overdose. If the Clinic Director feels the participant has taken an overdose, it should be reported as a serious adverse experience.

Expected adverse experiences. The FDA defines "expected adverse experiences" as those adverse experiences which have been identified in the Participant Information Booklet. A listing of "expected" adverse experiences for AREDS study medication is provided in Chapter 10.

Unexpected adverse experience. Unexpected adverse experiences are those which are NOT specified in the Participant Information Booklet or in Chapter 10.

Associated with use of study medication. A determination is made by the investigator as to what relationship, if any, the study medication has to the adverse experience. The assessment may change based on information which develops later in the study.

### 7.14.2 Reporting Requirements

Consistent with FDA regulations, it is the AER system policy that adverse experience reports should be submitted when the participant, a study investigator, or primary care physician believes a relationship exists between the adverse experience and the use of the study medication.

#### Adverse Experience

#### Reporting Requirements

|                                    |  |
|------------------------------------|--|
| Serious events                     | FAX the AER form to: 1-301-299-3991 (within 24 hours). Enter information into AREDS Interactive Data Entry System and transmit to the Coordinating Center. |
| All other adverse drug experiences | Enter and transmit AER form to Coordinating Center via the AREDS Interactive Data Entry System within 1 week of report.                                    |

1. All deaths must be reported by fax to the Coordinating Center within 24 hours of the report to the Clinical Center using the Death Report form.
2. Report adverse experiences according to the reporting requirements, irrespective of whether or not a dose reduction or discontinuation was necessary.
3. Adverse experiences may also require reporting to the local Institutional Review Board (IRB).
4. In addition to the required AER forms, the routine, required AREDS forms should also be completed.
5. The AER form specifies the parameters for determining the severity "grade" of the adverse experiences.
6. Chronic toxicities do not require reporting after the initial report, unless severity increases by one full grade.
7. An adverse experience with multiple manifestations (abnormal symptoms, abnormal laboratory results, and diagnosis) may be reported as a single adverse experience.

### 7.15 MANAGING ADVERSE EXPERIENCES

Adverse experiences may be reported during contacts with the participant (e.g. scheduled visits, nonscheduled visits, telephone calls, participant reports, or participant's physician reports). All adverse experiences will be reported to the Coordinating Center as described above. All adverse experiences should also be reported to the participant's private health physician. The Clinic Director or the participant's private physician may reduce or stop the study supplement at any time he or she

thinks such action is necessary to protect the participant's safety. Such events must be reported on the Protocol Anomaly form (Appendix C).

If an adverse experience of any grade is reported for a participant taking the Trial Medication, the Trial Medication may be discontinued for at least one week and may be reinitiated once the adverse experience has resolved. If the adverse experience recurs after the participant reinitiates the Trial Medication, or the Trial Medication is not reinitiated, the participant is ineligible for randomization.

The four steps listed below describing various dose and timing of Study Medication, are to be used to step-down the Study Medication if an adverse experience occurs following randomization.

- STEP 1: Study Medication discontinued.
- STEP 2: Two (2) tablets per day: One (1) in the morning with food and one (1) in the evening with food.
- STEP 3: Four (4) tablets per day: One (1) tablet about every 4 hours with food for a total of four (4) tablets per 24 hour period.
- STEP 4: Four (4) tablets per day: Two (2) tablets in the morning with food and two (2) tablets in the evening with food.

All AREDS participants will begin taking Study Medication according to the guidelines of STEP 4. Study Medication will be "stepped down" using the following guidelines.

- ! Life-threatening adverse experiences. Study Medication will be discontinued (STEP 1). Medication will only be re-initiated (STEP 4) if it is later determined that the life-threatening event is attributable solely to causes other than the Study Medication.
- ! Severe or moderate adverse experiences. Study Medication will be discontinued (STEP 1). If after 1 month without supplements the participant's condition has resolved and there are no medical contraindications, Study Medication will be reinitiated (STEP 2). If no reactions are observed after a 1-month period on the STEP 2 regimen, the participant should resume taking four (4) Study Medication as described in STEP 3 for the remainder of the study.
- ! If the participant experiences a severe adverse experience while following the regimen of STEP 2, the participant should be taken off Study Medication permanently. If the participant reports a severe or moderate adverse experience while on STEP 3, the participant should return to STEP 1 and proceed to STEP 2 and remain at STEP 2 for the study duration unless adverse experiences develop at this step.
- ! Mild adverse experience. Participant should be dropped a step and challenged for a month at the lower step. If the condition resolves the participant may be rechallenged at the higher step. If the condition returns while at the higher step the participant

should be returned to the step at which no adverse reactions were observed for the remainder of the study.

If the participant is not at STEP 4 due to an adverse experience, and it is later determined that the experience is attributable solely to causes other than the Study Medication, the participant may reinitiate medication at STEP 4. If the participant experiences a condition for which the Study Medication may be contraindicated (eg, copper deficient anemia, oxalate kidney stones), complete and permanent stopping of the Study Medication may be necessary. Unmasking is usually not necessary unless such knowledge will alter the choice of participant care. If the investigator or private physician believes unmasking is required to appropriately manage the participant then the following procedures should be initiated:

- ! The Clinic Director or participant's private physician, should call the Study Chairperson to request unmasking. The details will be discussed and if the Clinic Director continues to believe unmasking is required then the Study Chairperson will authorize the Coordinating Center to provide the information to the Clinic Director. If the Study Chairperson or Coordinating Center can not be reached, the Clinic Director may open the envelope containing the medication information for the participant's bottle number which was supplied by the Coordinating Center. Note: These envelopes must be maintained in a secure, locked file cabinet or drawer.
- ! The Clinic Director may provide Clinical Center staff with information about the Study Medication ingredients only if he or she believes it is necessary for the participant's best care. The staff should be urged to keep the information confidential.
- ! The participant should continue to be followed on the same study visit schedule.
- ! All cases of unmasking will be reported by the Clinical Center on the Protocol Anomaly form (Appendix C).

## **7.16 PROCEDURES FOR NON-AREDS PARTICIPANT VISITS**

During the course of AREDS some participants may relocate, become incapacitated, or experience other events which may make it difficult or impossible for them to visit the Clinical Center where they were enrolled for study scheduled visits. At a minimum, participants should be encouraged to be seen in the Clinical Center for the scheduled annual visits.

### **7.16.1 Participants Relocating Away From The Clinical Center**

Whenever possible, clinic staff should attempt to have the participant return to the Clinical Center for the scheduled annual visits. Participants willing to fly to the clinic at their own expense should be informed that the airlines will not necessarily discount fares for persons traveling for medically-related reasons; however, several airlines will waive some, or all, restrictions. These might include, but are not limited to:

- 1) not requiring a Saturday night stay to be entitled to a less expensive fare, and
- 2) allowing tickets to be purchased at any time prior to the flight at a fare equivalent to that of advance-purchase fares.

Some of the major airlines have representatives available to assist with special arrangements for persons traveling on medically-related business. Clinic staff should contact the carriers serving their area for more information.

Participants that relocate may be reluctant or unable to travel long distances to the clinic that originally enrolled/randomized them; however, they may be willing to be seen at another AREDS Clinical Center if that clinic is closer or easier for them to get to. The participant should then be transferred from the original AREDS clinic to the Clinical Center where they will be followed.

When it is not possible for a participant to be followed at an AREDS Clinical Center, clinic staff should attempt to make arrangements for that participant to be seen by an area eye care specialist. The AREDS clinic staff should supply the physician with a copy of the AREDS Annual or Nonannual Followup forms prior to the date of the visit, with the appropriate sections highlighted for completion, and a self-addressed, stamped, return envelope. The eye care specialist should attempt to gather the following information:

- 1) measure visual acuity
- 2) a clinical assessment of the lens and retina
- 3) fundus photographs (annual visit)
- 4) red-reflex photographs (annual visit)
- 5) hematocrit measurement (annual visit)

Clinical Center staff will mail to the participant the next six-month supply of Study Medication and a mailer for the participant to return any remaining Study Medication previously dispensed. Subsequent to the visit, the Clinic Coordinator will conduct a followup telephone interview with the participant, at which time a summary of the participant's recent medical history will be taken.

#### 7.16.2 Collaborating Ophthalmologists

AREDS has established a voluntary, nation-wide network of Collaborating Ophthalmologists, approved by the Operations Committee. Participating physicians have been provided with examination guidelines; specifically, the ophthalmologic data relevant to the study. Additionally, all participating Collaborating Ophthalmologists have received the book 'Guidelines for Collaborating AREDS Ophthalmologists' (June 1997) that includes a form to be completed at the time of the participant's examination and submitted to the referring AREDS Clinical Center. Guidelines for obtaining fundus photographs and Clinical Lens Grading Examples and Standards are also provided.

When Clinical Center staff become aware that a participant is relocating, it is their responsibility to ascertain if there is a Collaborating AREDS Ophthalmologist within a reasonable distance. The Clinical Center will refer the participant to the specific ophthalmologist and make the

appointment for the participant. Upon completion of a participant examination by the Collaborating Ophthalmologist, the AREDS Follow-up form (version 01, 05/28/97) is to be mailed to the referring Clinical Center, where examination data are entered into the AREDS data system. Fundus photographs are also to be mailed, with the Follow-up Form, to the referring AREDS Clinical Center, which will then forward them to the Fundus Photograph Reading Center.

AREDS Clinical Centers were provided with a 'Directory of Physicians Collaborating with The Age-Related Eye Disease Study' (June 1997), to assist them with locating physicians in a specific geographic location.

## **7.17 REPORTING OF HOSPITALIZATIONS**

A hospitalization is an event in which an individual is admitted to a hospital, regardless of the reason for the hospitalization. For each hospitalization of an AREDS participant, a Hospitalization Form should be completed and the Clinical Center should request the "hospital discharge summary" for that hospitalization from the hospital. When the Center has received this information, a copy of it should be sent to the Coordinating Center. When a surgical procedure was performed, the operative summary is not considered a substitute for the hospital discharge summary. Note the operative summary is not routinely required, but may be requested at a later date by the Morbidity and Mortality Committee. After discharge, any further hospitalizations for that participant are new events, ie, they are not continuations of the previous hospitalization.

## **7.18 REPORTING OF DEATHS**

When a participant dies, a death certificate is filed with the state health department or corresponding health authority in the decedent's state (or territory) of residence. Upon notification of the death, the Clinical Center must complete a Death Form, which is to be faxed to the Coordinating Center within 24 hours of notification. The Clinical Center must then obtain a copy of the official death certificate. Such certificates may be obtained from the hospital in which the death occurred (if it was an in-hospital death) or from the medical examiner/coroner for the locality where the death occurred.

## **7.19 AREDS CLINICAL LENS GRADING PROTOCOL - DETAILED PROTOCOL**

### **7.19.1 Overview**

The AREDS Clinical Lens Grading Protocol was developed for grading the presence and severity of nuclear, cortical and PSC lens opacities in a clinical setting. The simplified grading system requires minimal grader training for persons already proficient in the use of the slit-lamp. A careful reading of the protocol and close adherence to the grading instructions are needed to collect data in a uniform fashion.

## 7.19.2 General Instructions

- ! Dilation - Pupils should be dilated to at least 5mm.
- ! Grading of Opacities - The lenses are examined at the slit lamp with 10X magnification for the presence and severity of three types of lens opacity: nuclear opalescence, cortical opacity, and posterior subcapsular (PSC) opacity. For each type of opacity, the examiner compares the lens being examined with a series of three standard photographs of increasing severity. The standard photographs are combined onto one print, which can be held up or mounted next to the slit lamp for reference. The examiner determines whether the lens being examined has an opacity that equals one of the standard photographs or an opacity whose severity falls between the standard photographs. If the severity of the opacity falls between the standard photographs, a decimalized grade was assigned corresponding to the percent of the way the opacity falls between the standard photographs. In 1999, this procedure was changed to a three-level grade. Answers are recorded on the AREDS followup visit form by selecting the appropriate code numbers separately for right and left eyes. If the examiner cannot evaluate the lens for a particular type of opacity, a "8-cannot grade" code is provided.

## 7.19.3 Grading of Nuclear Sclerosis

- ! Nuclear Landmarks - In the normal or nonsclerotic lens, the "nucleus" consists of a central dark interval (sulcus), adjacent bean-shaped brighter areas (lentils--one anterior and one posterior to the sulcus), and brighter curved bands (lamellae, or nuclear surface bands) anterior and posterior to the lentils and separated from them by narrow dark bands. Although nuclear sclerosis standard 1 shows signs of moderate opalescence, many of these features are visible.
- ! Grading Rules - For grading the severity of nuclear sclerosis two factors are considered: 1) the optical density (sometimes described as "opalescence") of the nuclear landmarks, especially the sulcus, and 2) the definition of these structures (contrast between light and dark bands). Optical density is given greater weight. In the early stages of nuclear sclerosis, increased optical density is noticeable only in the normally dark bands, particularly the sulcus, but in advanced stages the density of all bands becomes greater. With increasing nuclear sclerosis, the definition of nuclear landmarks decreases, and finally disappears. **For grading nuclear status the primary consideration is the degree of reflectance (sometimes termed "opalescence") of the sulcus, with secondary consideration given to the definition of the nuclear features, i.e. contrast of the dark and bright bands.**
- ! Nuclear Standard Photographs - Three standard photographs with increasing amounts of nuclear opalescence are used for grading. In Nuclear Standard 1 the density of the sulcus has increased so that only a suggestion of the sulcus can be detected. Towards the upper and lower ends of the sulcus, segments of what appears to be the equator of the fetal nucleus (or a zone just beneath its surface) are visible as steeply curved white

lines. Only a small part of the anterior lentil is visible. The posterior nuclear surface band cannot be seen at all and the anterior one is very faint. In Nuclear Standard 2, the sulcus has become so dense that only a faint shadow marks its location at the center of the lens, and the entire nucleus has become dense enough that lentils and lamellae are not distinguishable. Nuclear Standard 3 shows a further increase in nuclear density, to the point that neither the sulcus nor other features are distinguishable.

! Slit Lamp Settings - Grading of nuclear opalescence is done with the illuminating beam of the slit lamp angled at  $45^{\circ}$  to the viewing axis, the slitbeam width set at 0.3mm and the slitbeam height set at 9mm.

! Codes for Nuclear Grading - Decimalized nuclear grades were originally assigned as follows:

0.0 = No nuclear opacity  
 1.0 = Nuclear Standard 1  
 2.0 = Nuclear Standard 2  
 3.0 = Nuclear Standard 3  
 4.0 = Completely opacified  
 8 = Cannot evaluate

If you believe the severity of the opacity is between two standard photos, estimate the percent of the way between the two standards; e.g., halfway between 1 and 2 would be 1.5. If the severity of the opacity is greater than the last standard, estimate the percent of the way between the last standard and a completely opacified lens, e.g., 3.8 or 3.3.

In 1999, scores were changed to:

1 = If < Standard 2  
 2 = If  $\geq$  Standard 2, < Standard 3  
 3 = If  $\geq$  Standard 3  
 8 = Cannot grade

#### 7.19.4 Grading of Cortical Opacities

! Grading Rules - Grading of cortical opacities is done at the slit lamp using a red reflex image. The slit beam height and width are set by the examiner according to his/her usual practice as long as retroillumination is obtained. The position may be changed as needed so that all areas of the lens can be viewed against the red reflex. With retroillumination cortical opacities appear darker than the adjacent red reflex. An area is considered involved by opacity if it is definitely more opaque than adjacent uninvolved areas. Opacities not seen against the red reflex are not counted. For comparison with the standard photographs, all areas of opacity are mentally rearranged into a contiguous mass and the total area of involvement is compared with the standard photographs. Vacuoles (small round cyst-like features) are not considered to be part

of cortical opacity unless they are organized, e.g., part of a linear formation. When determining the extent of involvement, sizable clear areas bounded by opacity are subtracted from the total. Areas occupied by posterior cortical opacities that are not overlapped by anterior cortical opacities are added to obtain the total area of involvement. The density of opacity is not taken into account. Cortical and PSC opacities are differentiated from each other mainly by location, and secondarily by configuration.

- ! Cortical Standard Photographs - Cortical opacities typically are wedge-shaped and radially oriented, extending from the periphery toward the center. Their appearance varies from dense opacity to diffuse collections of dots separated by clear areas.

Three standards with increasing amounts of cortical opacity are used for grading cortical opacities. In each standard the dashed white line defines the margins of the opacities. In cortical opacity Standard 1, three small spokes project in from the periphery between 5 and 7 o'clock, with a clear space between the spokes at 5:00 and 5:45. In Standard 2, a pie-shaped wedge extends from 3 to 6 o'clock, with a separate small spoke at 2:30. Standard 3 shows a semi-circle of cortical opacity extending from 3:30 to 9:30, with a dense spoke projecting from it centrally, and a group of vacuoles near the 3:30 margin (included as opacity because they are organized).

- ! Codes for Cortical Grading - Grading of cortical opacities is done by comparing the proportion of pupillary involvement with cortical opacities in the lens to be graded and the proportion of involvement in the standard photographs. **Only opacities seen against the red reflex image are counted.**

Decimalized cortical grades were originally assigned as follows:

- 0.0 = No cortical opacity
- 1.0 = Cortical Standard 1
- 2.0 = Cortical Standard 2
- 3.0 = Cortical Standard 3
- 4.0 = Completely opacified
- 8 = Cannot evaluate

If you believe the severity of the opacity is between two standard photos, estimate the percent of the way between the two standards, e.g., one-third of the way between 1 and 2 would be 1.3. If the severity of the opacity is greater than the last standard, estimate the percent of the way between the last standard and a completely opacified lens, e.g., 3.9.

In 1999, scores were changed to:

- 1 = If < Standard 2
- 2 = If  $\geq$  Standard 2, < Standard 3
- 3 = If  $\geq$  Standard 3
- 8 = Cannot grade

## 7.19.5 Grading of PSC Opacities

- ! Grading Rules - Grading rules are similar to those for cortical opacities (See Section IV. A.), except that the red reflex image is focused at the plane of the posterior capsule. In this position the pupillary margin should be blurred. PSC opacities are considered to be present only when an area is definitely more opaque than adjacent areas as seen against the red reflex. For comparison with the standard photographs, all areas of PSC opacity are mentally rearranged into a contiguous mass and the total area of involvement is compared with the standard photographs. Mittendorf dots are disregarded. The density of PSC opacities is not taken into account.
- ! PSC Standard Photographs - PSC opacities are seen just beneath the posterior lens capsule. Frequently they are centered near the posterior pole of the lens. Although they usually appear as a lacy configuration which may contain vacuoles (any such are considered part of PSC), they may range from a darkly opaque network to a barely discernible diffuse haze. Because PSC opacities are fairly compact with few clear areas, small spaces within PSC are not subtracted from the estimate of extent. Three standard photographs with increasing amounts of PSC opacity are used for grading PSC opacities. In each standard the dashed white line defines the margins of the opacities. In PSC Standard Photograph 1, a roundish opacity is located just left of center in the photograph. In PSC Standard 2 a larger opacity, also left of center, includes vacuoles around nearly half of its perimeter. Within its margins of the density of the involved area is uneven, but the entire region is considered opacified. PSC Standard 3 shows a roundish opacity that is even larger and involves the center of the lens. (An array of cortical spokes, located peripherally between 6:30 and 10:00 and rather unfocused, is not considered part of PSC.)
- ! Codes for Grading PSC Opacities - PSC grading is done by comparing the size of the PSC opacity in the lens to be graded with the size of the PSC opacity in the standard photographs. **Only opacities seen against the red reflex image are counted.**

Decimalized PSC grades were originally assigned as follows:

- 0.0 = No PSC opacity
- 1.0 = PSC Standard 1
- 2.0 = PSC Standard 2
- 3.0 = PSC Standard 3
- 4.0 = Completely opacified
- 8 = Cannot grade

If you believe the severity of the opacity is between two standard photos, estimate the percent of the way between the two standards, e.g., two-thirds of the way between 1 and 2 would be 1.7. If the severity of the opacity is greater than the last standard, estimate the percent of the way between the last standard and a completely opacified lens, e.g., 3.2.

In 1999, scores were changed to:

- 1 = If < Standard 2
- 2 = If  $\geq$  Standard 2, < Standard 3
- 3 = If  $\geq$  Standard 3
- 8 = Cannot grade

## 7.20 HOME VISITS

In the event that a participant is unable to be followed at an AREDS Clinical Center or other eye care specialist, he/she may be visited at home by an AREDS ophthalmologist and/or a certified staff member from the clinic. At the least, a visual acuity and refraction might be obtained utilizing either the ETDRS Charts R, 1, and 2, and a trial lens set, or some other, more portable, device for measuring visual acuity. In the event that an ophthalmologist participates in the home visit, it is expected that some assessment of lens and retinal status might be obtained utilizing an ophthalmoscope. Other procedures might be undertaken at such a visit; however this would be dependent upon staff and instrumentation availability, in addition to the ability of the participant to tolerate the procedure(s). The staff should take with them the following items:

- 1) trial frame and set of loose lenses
- 2) AREDS visual acuity charts (Charts R, 1, and 2)
- 3) a locking tape measure for 4- and 1-meter lanes
- 4) ophthalmoscope
- 5) mydriatic drops
- 6) six month supply of Study Medication
- 7) hand-held slit lamp (if available)
- 8) appropriate AREDS forms

## 7.21 VISUAL FUNCTION QUESTIONNAIRE (VFQ)

AREDS will assess vision-targeted health-related quality of life in all AREDS participants. These data will be used to describe vision-targeted health-related quality of life in a cohort of patients with a range of AMD and cataract severity from no measurable disease to advanced disease. Data will be collected through several interviews. The 5-year visit interview provides data for the clinical trial (assuming balance at baseline) and the interview three years post the first interview provides natural history data (change from first interview to interview three years later). The interview at the last followup visit potentially provides a range of cohorts with intervals between interviews ranging from 5 to 7 years under current funding.

### 7.21.1 The NEI VFQ-39

The University of Southern California and the RAND Corporation, under NEI sponsorship, developed a visual function questionnaire, the NEI VFQ, to assess vision-targeted health-related quality of life. The primary questionnaire has 25 items (VFQ-25). An additional 14 items are

available that, according to the developers, enhance the reliability of the vision sub-scales and are likely to improve the responsiveness of the sub-scales to an intervention over time (VFQ-39). The VFQ-39 has been chosen for AREDS and is expected to take 15 to 20 minutes to complete.

The NEI VFQ covers areas of functioning and well-being for persons with eye diseases, and consists of questions that should be relevant to the majority of visually impaired adults regardless of the underlying cause of their visual problem. The questions generate sub-scales for 11 dimensions of vision-targeted health-related quality of life: overall vision, near vision, distance vision, social functioning limitations, role limitations, dependency, mental health, driving, peripheral vision, color vision, and ocular pain. Additionally, two questions are included (in VFQ-39) pertaining to a general health rating. The VFQ-39 is a shortened version of a 52-item field test questionnaire<sup>7,8</sup>, whose content was derived from preliminary field testing and an analysis of transcripts from 25 same eye-condition focus groups.

#### 7.21.2 Interview Administration

- ! The VFQ will be administered by interview to all AREDS participants at their next scheduled visit beginning Fall 1997 (if at least one year from the 5-year visit), at the 5-year followup visit, three years following the first interview, and at the final followup visit.
- ! Interviews will be administered by a trained staff member at each Clinical Center. The interviewer will be trained by personnel from the Coordinating Center.
- ! The Coordinating Center will create a schedule for interviews for each participant.
- ! The Clinical Center will mail the original completed questionnaires to the Coordinating Center for processing.

#### 7.21.3 Analysis Plan

Responses are recoded on a scale from 0 to 100, where 100 always defines the most favorable vision-targeted health-related quality of life. The sub-scales that define a particular dimension of vision-targeted health-related quality of life, e.g., near vision, are averaged to create 12 scores per patient (including the general health rating) that range from 0 to 100. Items that are left blank (missing data) are not included when calculating scores.

7.21.3.1 Study of Clinical Course. The distribution of scores for each dimension, stratified by year of followup and treatment assignment, will be described for (1) each AMD Category and (2) participants without a history of cataract versus participants with a history of cataract surgery or a definite lens opacity.

The distribution of the difference in the scores measured at the first interview compared to the second interview and third interviews (if performed), stratified by number of years between

interviews, will be described for (1) development of an AMD event, (2) development of a lens event, and (3) each intervention.

7.21.3.2 Clinical Trial. The distribution of scores at 5 years will be compared by intervention. This analysis assumes scores at baseline were balanced across the four interventions. Rate of change in score will be compared by treatment, stratified by years between interviews.

7.21.3.3 Analysis Methods. Distributions of scores and differences in scores will be described and comparisons between disease categories and treatment will be made using rank score methods. Logistic regression will be used to analyze possible associations between scores and development of an AMD or lens event. Adjustments for multiple comparisons (e.g., Bonferroni) will be applied to the results.

## 7.22 END-OF-TRIAL CLINIC/HOME VISIT GUIDELINES

Home visits are a means for obtaining study data before the end of the clinical trial from participants who do not now come to the clinic, but who still live in the clinic area and with whom the study coordinator maintains some contact. The primary goal is for participants to come to the clinic for examination, and contacts by the coordinator including a visit to the home should have that as first priority. The coordinator knows her/his participants and should exercise judgment regarding participant cooperation and rapport. The home visit should be done by a team of two persons for security and to facilitate visual acuity examination in the home environment.

### 7.22.1 Clinic Visits

If in the coordinator's judgment it is reasonably likely that a participant will cooperate with at least one of the listed examination procedures once in the clinic, then the coordinator may provide for the necessary transport and other assistance. The clinic procedures for end-of-trial visit in priority order are:

- ! Visual acuity (with refraction if possible)
- ! Retinal photography
- ! Lens photography
- ! Annual/closeout visit form
- ! Follow-up interview (if not done in last 12 months)
- ! VFQ (if not done in last 12 months)
- ! If participant refuses further follow-up:
  - Collect study medications
  - Obtain address to which final trial information should be sent

Photography may not be done if dilation is refused or contraindicated. If photography cannot be done, clinical evaluation of the retina and lens should be attempted, without dilation if necessary. Collection of other data, including by interview, should be done with discretion to maintain cooperation. Clinics are authorized to provide assistance to participants going to the clinic.

### 7.22.2 Home Visits

Whether or not the home visit leads to scheduling a clinic visit, two procedures should be done in the home: visual acuity and VFQ. ETDRS Visual Acuity Charts 1 and 2 should be used, in a bright light setting if possible. Avoid direct light reflection off the surface of the chart toward the participant's eyes. The test should be done using as correction the refraction of record, updated at the visit if possible. Update refraction by using a trial frame and lenses for the refraction of record, and a limited set (at least the previous refraction and 1D increments of plus and minus sphere and cylinder) of trial lenses. Use Chart R. A pinhole may be used over the current glasses to assess whether this improves the visual acuity results. If a four-meter lane cannot be used, the test may be done at 3.2, 2.5, or 2 meters and the distance noted on the data form.

If the home visit team includes an ophthalmologist, clinical evaluation of the retina and lens may be done through undilated or preferably dilated pupils of willing participants, by direct or indirect ophthalmoscopy, or hand-held slit illuminator. If the VFQ cannot be administered in the home, it may be administered by telephone. Collection of other data, including by interview (i.e., follow-up interview, annual visit form information), should be done with discretion to maintain cooperation.

Materials to bring for a home visit:

- ! AREDS home visit examination form
- ! VA worksheet; AE, hospitalization and protocol anomaly forms
- ! Follow-up interview
- ! VFQ
- ! ETDRS charts 1, 2, and R; tape measure
- ! Equipment for ophthalmic exam (including dilating drops), if applicable
- ! Medications and supplemental form, if applicable
- ! Trial frame and appropriate lenses for refraction

### 7.23 REFERENCES

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Examination Survey, 1976-1980. Vital and Health Statistics. Series 1, no.15. Washington, DC: US GPO, (DHEW Publication No. (PHS) 81-1317), 1981.

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**Exhibit 7-1. ETDRS CHART EQUIVALENT VISUAL ACUITY MEASUREMENTS**

| Expected score | <u>Approximate Snellen visual acuities<sup>1</sup></u> |          |          |         | Decimal fraction | LogMAR |
|----------------|--|----------|----------|---------|------------------|--------|
|                | 1 meter  | 4 meters | 6 meters | 20 feet |                  |        |
| 34-38          | 1/10   | 4/40     | 6/60     | 20/200  | 0.10             | +1.0   |
| 39-43          | 1/8  | 4/32     | 6/48     | 20/160  | 0.125            | +0.9   |
| 44-48          | 1/6.25   | 4/25     | 6/38     | 20/125  | 0.16             | +0.8   |
| 49-53          | 1/5  | 4/20     | 6/30     | 20/100  | 0.20             | +0.7   |
| 54-58          | 1/4  | 4/16     | 6/24     | 20/80   | 0.25             | +0.6   |
| 59-63          | 1/3.15   | 4/12.6   | 6/20     | 20/62.5 | 0.32             | +0.5   |
| 64-68          | 1/2.5  | 4/10     | 6/15     | 20/50   | 0.40             | +0.4   |
| 69-73          | 1/2  | 4/8      | 6/12     | 20/40   | 0.50             | +0.3   |
| 74-78          | 1/1.6  | 4/6.4    | 6/10     | 20/32   | 0.625            | +0.2   |
| 79-83          | 1/1.25   | 4/5      | 6/7.5    | 20/25   | 0.80             | +0.1   |
| 84-88          | 1/1  | 4/4      | 6/6      | 20/20   | 1.00             | 0.0    |
| 89-93          | 1/0.8  | 4/3.2    | 6/5      | 20/16   | 1.25-            | 0.1    |
| 94-98          | 1/0.625  | 4/2.5    | 6/3.75   | 20/12.5 | 1.60             | -0.2   |
| 99-100         | 1/0.5  | 4/2      | 6/3      | 20/10   | 2.00             | -0.3   |

<sup>1</sup>Snellen fraction determined from the lowest line read with one or fewer mistakes. This is similar to allowing one mistake per line. If the participant makes more than 1 mistake on the 20/800 line and on all subsequent lines, then the Snellen fraction should be recorded as 20/800. Note the actual score may vary from the expected scores listed.

Source: Ferris FL, Kassoff A, Bresnick GH, et al: New visual acuity charts for clinical research. *Am J Ophthalmol* 94:91-96, 1982.

**Exhibit 7-2. 95 PERCENT CONFIDENCE INTERVALS AND WIDTHS FOR  
VARIOUS NUTRIENTS FOR SAMPLES OF SIZE 50 AND 200**

| Nutrient                    | RDA * | Average              | Standard Deviation | Sample size    |                |
|-----------------------------|-------|----------------------|--------------------|----------------|----------------|
|                             |       |                      |                    | 50             | 200            |
| Vitamin E (TE) <sup>1</sup> | 30    | 7.68 <sup>2</sup>    | 0.4                | (7.57, 7.79)   | (7.62, 7.74)   |
| Width                       |       |                      |                    | 0.22           | 0.12           |
| Vitamin A (IU)              | 5,000 | 8,550 <sup>3</sup>   | 4226               | (7,379, 9,721) | (7,964, 9,136) |
| Width                       |       |                      |                    | 2,342          | 1,172          |
| Vitamin C (mg)              | 60    | 103.5 <sup>4,5</sup> | 111.6              | (72.6, 134.4)  | (88.0, 119.0)  |
| Width                       |       |                      |                    | 61.8           | 31.0           |

\* Recommended Daily Allowance.

<sup>1</sup> Tocopherol equivalents.

<sup>2</sup> Coates RJ et al. An evaluation of a food frequency questionnaire for assessing dietary intake of specific carotenoids and vitamin E among low-income black women. *Am J Epidemiol* 1991;134:658-671.

<sup>3</sup> Willett WC et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51-65.

<sup>4</sup> National Center for Health Statistics. Dietary Intake Source Data: United States, 1976-80. Health Vital Stat Series, No. 231, DHHS Publication (PHS) 83-1881, 1983.

<sup>5</sup> Average of data for men and for women, 55-64 and 65-74 years of age, with income above poverty level.