# Incidence of Macular Degeneration in Older Women

# Manual of Procedures

## August 22, 2002

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## 1.1 OVERVIEW

Age-related macular degeneration is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors such as prior cataract surgery with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the impact of late ARM on vision-targeted health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5,482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5% of these women have photographically validated late ARM, 41.5% have early ARM, and 54% have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEI-VFQ. The eye examination will consist of measurements of visual acuity using Bailey-Lovie targets with habitual correction, contrast sensitivity testing, autorefraction, and measurement of intraocular pressure. After dilation, photographs of the fundi will be taken. All of these data will be used to determine the incidence of macular degeneration in older women. All film from fundus photography will be forwarded to the Senior Photographer, Colleen Gillis, whom will have the film developed and will monitor data quality. The UCLA Reading Center will establish a photographic archive for SOF, from which the incidence of AMD will be assessed. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-Related Maculopathy Grading System (WARMGS) in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30% of the eyes with ARM and 10% of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

## 1.2 ORGANIZATION

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# PROCEDURES FOR OCULAR EXAMINATIONS

## 2.1 INTRODUCTION

The purpose of the eye examination is to determine whether there is evidence of age-related macular disease. During the examination, the examiner will perform visual acuity testing, contrast sensitivity testing, intraocular pressure measurement, and photography after dilation. Photographs of the fundus or back of the eye will be taken using a Canon non-mydriatic camera.

In a large study such as this, there is great opportunity for potential errors to become manifest. This is particularly true when more than one examiner participates in the study. As you are all well aware from previous examinations in the Study of Osteoporotic Fractures, a subject examination performed as part of a study must be conducted in a different fashion and different frame of mind than a clinical office examination.

A study subject must be examined according to a set procedure that cannot vary from subject to subject or with time. The technique of examination and criteria for filling out the examination forms must be identical for all examiners participating in the study. The protocol must be strictly followed and extreme care must be taken in examining the subject. It is recommended that the protocol be reviewed periodically to keep these points fresh in your memory. The protocol is necessarily long in order to maintain consistency and reduce examiner variability, and to provide a reference guide as you begin to collect data.

When filling out the forms, please use blue or black ink. Please do not use either pencil or red ink. In most instances, data recording involves writing the appropriate code for each item being assessed in the

proper box. When errors in the recording are made, do not write over the initial entry, but cross it out and write the new entry above or to the side. If an entry becomes too confusing for the coder to understand, make a comment to the side of the box describing the correct entry.

### 2.1.1 Introduction for Participants

Subjects should be told to wear the eyeglasses they usually wear for driving or watching TV (distance activities). If they wear contact lenses and their distance glasses have not been recently changed, they should wear their contact lenses. Subjects who have had recent eye surgery should be encouraged to participate at least 30 days after their surgery. **Please remind all subjects to bring their eyeglasses.**

### 2.1.2 Backup Examiners

Backup examiners should do the complete exam on at least one subject a week so that he/she maintains his/her skills.

## 2.2 SUBJECT IDENTIFICATION

The subject's SOF record number, date of birth, date of examination and place of examination will be filled in when the subject is first registered for the eye examination. Make sure that the visit is marked as a home visit or a clinic visit on the Visit 8 Checklist (Page 0 of the clinic visit forms).
Prior to beginning the exam, the examiner will determine the status of both eyes by asking the following questions, which are included in depth on the vision interview, ocular history and medication forms (p.2-5):

Vision Interview

1. At present time, would say your eyesight (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor, or are you completely blind?
2. How much of the time do you worry about your eyesight?
3. Are you currently using eye drops in your eye for any reason?
4. Have you ever used eye drops prescribed by a doctor to lower the pressure in your eyes?
5. Have you ever been hit in the eye with a fist or an object?

The next questions are about how much difficulty, if any, you have doing certain activities while wearing your glasses or contact lenses, if you use them for this activity.

6. How much difficulty do you have reading ordinary print in newspapers?
7. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools?
8. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs, in dim light or at night?
9. How much difficulty do you have driving during the daytime in familiar places?

10. Are you limited in how long you can work or do other daily activities such as housework, child care, school, or community activities because of your vision?
11. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
12. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

Ocular History

1. Has a doctor ever told you that you had any of the following?
    a. Cataracts?
        a1. Cataract extraction (surgery)?
        a2. Combined cataract/glaucoma surgery?
        a3. If YES to b or c, during cataract surgery was a new lens placed in your eye?
        a4. Yag capsulotomy or treatment for 2nd cataract in the same eye?
    b. Glaucoma?
    c. Macular degeneration?
    d. Uveitis (inflammation of the eye)?
    e. Stroke or hemorrhage of the eyes?
    f. Diabetes in the eyes?
    g. Blind eye?
1. Have you ever had eye surgery or laser treatment other than cataract surgery?
    a. Laser surgery for diabetes?
    b. Laser surgery, photodynamic therapy or other procedures for macular degeneration?
    c. Glaucoma surgery, including laser surgery for glaucoma?
    d. Retina surgery?
    e. Corneal graft or transplant?
    f. Refractive surgery (a procedure that allows you to either not wear glasses, or to wear less powerful ones)?
    g. Enucleation (removal of eye)?
    h. Other eye surgery?

Please be sure to return to the Vision Checklist (Page 1 of the forms) and mark your rating of the ocular history and any comments you feel are relevant. If the subject is not sure of the date and year of surgery or diagnosis date ask to give their best guess.

### 2.2.1 Letter Literacy Test May Be Ignored

## 2.3 BAILEY-LOVIE VISUAL ACUITY TESTING

a. Illumination: It is important that all of the vision tests be performed in areas of UNIFORM illumination, e.g., no abrupt changes in illumination or shadows when moving a few feet or changing orientation. Diffuse natural light, fluorescent light or a combination of the two is best. The chart luminance test should result in a luminance reading of 50-70 ft-Lamberts (10.4 to 11.0) on the Sekonic Zoom Meter for each of the two tests performed in the office. The light meter should be used to standardize chart luminance. If natural light levels vary considerably during the day or from day to day you should check luminance levels for each participant. If the luminance levels are stable you may check it once each morning before the first participant. The spatial relation of the targets to the subject should be positioned in such a way as to **minimize glare** on target surfaces. Determine the optimal positioning through trial and error under a range of naturally varying light conditions.

b. Distance: The test is administered with the subject seated 10 feet from the target. This distance should be marked on the floor with tape. Measure from the target to the middle of the chair.

c. Glasses: Acuity is tested with habitual correction for distance vision.

Before testing vision, ask the subject if she normally wears glasses, or contact lenses, or both for distance vision. (Probes: "Do you wear glasses to see things far away, like when you go to a movie theater or when you drive a car?") If she answers that she has glasses for distance but sees better without them, distance tests should be performed with her wearing her glasses. When scheduling subjects for visits, remind them to bring or wear the glasses that they use most often for distance vision. If she wears glasses, please identify if she wears distance only, bifocals, or no line bifocals (trifocals, progressives, or any multifocal eyeglasses will be marked as "bifocals," or "no line bifocals" on the form [p. 17]).

### 2.3.1 Visual Acuity (Bailey-Lovie Visual Acuity Charts)

Introduction:

The Bailey-Lovie visual acuity letter charts incorporate the following features:
a. geometric progression of letter size;
b. near equal legibility of all letters in the chart;
c. each row has the same number of letters (5);
d. between row spacing is equal to the height of the letters in the smaller row;
e. letter spacing is equal to one letter width.

These features ensure that the visual acuity task is essentially the same for all letter sizes so that the angular size of the letters is the only parameter that differs, which determines the visual acuity

score. This combined with letter size progression on a uniform logarithmic scale, allows for acuity testing at optional non-standard distances determined by the progression of letter sizes. We are assessing acuity at 10 feet. The size of the chart is reduced to produce standard scores at this critical viewing distance. (See Bailey IL, Lovie JE. New design principles for visual acuity letter charts. Am J Optom Physiol Optics 53(11): 740-745, 1976.)

### 2.3.2 Equipment

a. Bailey-Lovie Letter Chart
b. Occluder
c. The Sekonic Zoom meter will be used to test illumination in the office (Home Visits will not require checking the lighting for the visual acuity chart because it is a lighted Goodlight box).

Please use the instructions for the Sekonic Zoom meter:

### 2.3.3 Measurement Procedures

a. At all times, check the vision in the right eye first.

b. The target should be placed at approximately the eye level of seated subjects. Seat subject on straight-backed chair, 10 feet from the midline of the body target.

c. If the subject wears glasses (bifocals or regular glasses) for distance viewing, such as driving, walking or at a theater, test her vision with her wearing her glasses. If she only wears glasses (bifocals or regular) when she reads, test distance vision at 10 feet without glasses. Test contact lens wearers with their lenses on the eyes. If a subject says that she wears glasses but sees better without them, test WITH THEM (her "normal" state).

d. Ask the subject to hold the occluder so that her left eye's vision is blocked and only the right eye can be tested. Then ask the subject to start reading the letters on the chart starting with the row with the double bar, proceeding down the chart toward the smaller letters. Say:

"Please read aloud the letters on this chart, read from left to right. Don't squint and don't lean forward. Start at the row with the double bar and read down as far as you can."

**If she reads the row with the double bar without errors, then say:**

"OK (begin/continue)."

e. As the subject reads, keep a running tally of the total number of letters missed by drawing a line through the letters read incorrectly.

f. When it is apparent that the subject is struggling (e.g. misses 2 letters on a row or goes very slowly) say:
"I want you to try reading the next row even if you just have to guess"?

If she misses 3 letters on any row, stop. If she says, "That's all," in the middle of a row, have her guess at the rest of the row (unless she has already missed 3 letters). Draw a line through the first row not attempted.

**If she cannot read the row with the double bar without one or more errors, then say:**

"How about the top row? Can you read that one?"

If she says no or reads it with error, then test at 5 feet (low vision distance) using the same procedure. Be sure to record that you are testing at 5 feet on page 17 of the forms.

g. For subjects that cannot see the chart at 5 feet, you need to test their vision with your fingers. Finger counting is tested by holding two or three fingers two feet from the subject and should be recorded as 96. Hand motions is tested by moving a hand back and forth in front of the subject with the other eye occluded. This should be recorded as 97. Light perception is tested by carefully occluding the fellow eye and directing the light of the penlight at the subject's eye from about one-foot distance. This should be recorded as 98. No light perception should be recorded as 99 on page 17 in the location where it says number of letters read correctly

h. REMEMBER TO RECORD THE NUMBER OF LETTERS READ CORRECTLY. The number next to each line on the score sheet is the number of all the letters from the top row to that row. So, if a subject attempted to read up to the line marked 40, she read a total of 40 letters. Compute the number of letters she read correctly by subtracting the number of letters crossed off from the number on the last line read e.g. 40 -5 crossed off = 35 correct.

i. For your information: with the Bailey-Lovie chart, the logarithm of minutes of arc (Log MAR) is computed according to the formula Log MAR = 1.1 - [(55n).02], where n = total letters missed. Snellen fraction equivalents can be obtained from the Log MAR scale along the side of the chart. They can also be obtained directly from the number of errors and the testing distance. You can tell the participants their acuity score in a form they will understand by locating it along the side of the chart.

j. The subject now holds the occluder so that the vision from the right eye is blocked. Steps d-i are repeated for the left eye.

## 2.4 Contrast Sensitivity

### 2.4.1 Equipment

VISTECH VCTS 6500 wall chart and the Sekonic L508 Zoom light meter. Mark the right and left hand sides of chart with a large R and L, clearly visible to the subject.

### 2.4.2 Description

Vision is generally measured by acuity tests that determine the smallest detail that can be seen, such as black letters on a white background. However, our everyday visual world contains objects that have varying levels of contrast (the level of black and white parts of an object and background) and a range of sizes. Those objects must often be seen under visually degraded conditions such as nighttime, fog, or rain. Contrast sensitivity measurements are needed to determine an observer's ability to see a wide range of everyday objects under normal and visually degraded conditions. Because any object can be decomposed into a combination of simple patterns, called sine waves, contrast sensitivity to sine waves provides a generalized measure of visual sensitivity to everyday objects.

The VISTECH contrast sensitivity test system, Model 6500, uses highly controlled photographic and printing techniques to present a series of sine wave gratings at calibrated levels of contrast. In a manner similar to reading the typical acuity chart, the observer simply reports whether or not a grating is visible; and if visible, at what orientation of all grating sizes. At the 10 foot distance, this spatial frequencies tested can be made higher or lower by simply changing viewing distance.

### 2.4.3 Illumination

The VCTS is designed so that it can accurately measure contrast sensitivity under normal room illumination corresponding to a chart luminance of 50-70 ft-Lamberts. For consistent measurement of contrast sensitivity, luminance must be kept constant from one area of the chart to another, and from one test to the next.

### 2.4.4 Light Meter Instructions

1. Please use the instructions with the Sekonic Zoom Meter.

2. If your test area has significant natural light, evaluate chart illumination under a variety of naturally varying conditions to determine if additional artificial light will sometimes be needed, especially at different times of day.

**Administration**

a. At all times measure the contrast sensitivity in the right eye first.

b. Place chart system in an area where it receives uniform lighting. Shadows or glare on the chart can affect contrast sensitivity measurement. To minimize glare, the chart should not be facing a window or have a window directly behind it. Measure chart luminance to insure lighting conditions is within desirable limits (see Light Meter Instructions).

b. The subject should be seated 10 feet from the chart, with the middle of the chart around eye level. TEST WITH GLASSES ON IF SHE WEARS GLASSES FOR DISTANCE. Mark the appropriate circle on page 6 of the forms packet to describe the subject's glasses.

c. Tell the subject: "This test measures your contrast sensitivity, or how well you are able to see differences in shades of dark and light. Your ability to see these bars relates to how well you see everyday objects."

"Can you see the light and dark bars on the top, left patch, (A1)?" (If "no", ask if she can see C1. If unable to see the bars on C1, then follow instructions for low vision.) Then tell the patient that "each row contains a different size bar pattern."

"The bars will be slanted slightly to the left, slanted slightly to the right, and straight up. Some patches are blank." Use large motions to demonstrate this with your hand.

"Your task is to read across each row, starting at row A. Patch 1 and call out whether the patch is pointing to the left, right, straight up and down or blank. Some of the patches are very low in contrast and you may not see any bars in these patches. If this is the case, simply answer 'blank'. However, if you do see something in a patch, but you are not sure which direction the bars are pointing, you are allowed to guess."

d. Scoring: Record the subject's response for each patch in the appropriate place on the scoring sheet by drawing a line through those called out incorrectly. Circle the patch number just before the first incorrect one on each line. This is the score for that line.

Point at each circle. Ask about every circle without stopping. Cross out the first one missed then circle the one just before that. Continue testing on the next row until one circle is missed, then cross that one out and circle the one before that was read correctly. Repeat for every row on the chart. Score each row before going on to the next.

e. Now test the left eye

f. Transpose the scores for both eyes from the worksheet to page 6 of the vision forms.

**Low Vision:** If the subject cannot see the bars in patch C1, mark the box for low vision on the scoring sheet and test at 5 feet.

For low vision, a quantitative measure of the subject's visual capability in terms of contrast sensitivity is accurately obtained at 5 feet. The spatial frequencies change in direct proportion to distance. (For example, at a 5ft. viewing distance, the spatial frequencies are .75, 1.5,3,6, and 9 cycles per degree).

## 2.5 PROCEDURE FOR OBJECTIVE REFRACTION USING THE HUMPHREY AUTOREFRACTOR

Overview:

The Humphrey Automatic Refractor 530, 560, or 570 is an automatic instrument that provides a fast, accurate objective refraction in seconds. The Automatic Refractor is easy to use. The operator takes only a few simple steps to align the patient, and then the instrument's auto-tracking mechanism takes over. A single push of the MODE button initiates the refraction cycle and prints the patient's prescription.

### 2.5.1 Objective Refraction

An objective refraction is a measurement of refractive error that requires no response from the subject. The equipment makes an objective measurement.

An objective refraction may be performed using the READ sequence. READ permits the taking of final acuities and the measurement of a single eye.

a. Set up the refractor.

1. If this is the first refraction of the day, remove the dust cover and the lens cover. Turn the refractor on.

2. If this is not the first refraction of the day, press CLEAR before beginning to refract a new subject.
3. For every subject, clean the chin and forehead rest areas with an alcohol swab. Remove the top chin paper to expose a fresh one.

b. Position the subject.

1. Make sure the subject is seated comfortably with his or her chin and forehead resting firmly in the subject support system. (The subject's glasses should be **off** for the refraction.)
2. Use the chin rest knob to raise or lower the chin rest until the subject's eyes are lined up with the silver marker on the forehead rest.
3. Since you are using READ, press Right Eye (R. EYE), to indicate that the right eye is to be tested first.
4. Ask the subject to look at the acuity chart while you look at the subject's eye through the viewing window.
5. Use the control ball to position the blinking green alignment light in the middle of the pupil and let go. The Refractor will then make an automatic vertex adjustment for the subject. You should observe that the instrument has positioned the green light between the two yellow lights.
6. Perform an Objective Refraction by pressing READ.
7. Once you have the refraction, then measure visual acuity and enter on the form for the refraction. Subjects can only miss one letter in a given row to get credit for that row. If the subject was successful at the 20/30 line, move down to the 20/25 and then to the 20/20 line. Record the results for the right eye.
8. When the Refractor has completed its measurement cycle, press PRINT. The print out will show the visual acuity measurements that you arrived at with the subject. Be sure that you are on the row "best" read.
9. Record the refraction on the form for "Autorefraction" (page 10).

To initiate the refraction for the left eye select the left eye, (L. EYE).

Repeat the same procedures, # 4-9, for the left eye.

Print the information, add the subject's study number and the date, keep the printout with the vision forms, but do not send the printouts to the UCLA CC.

## SCRIPT for AUTOREFRACTOR

"Mrs._____, I would like you to remove your eyeglasses and place your chin in the chin rest. You will be reading letters from left to right. The machine will try to make your vision sharper than your eyeglasses. We will first test your right eye."

"Now, we will repeat the test for your left eye."

## 2.6 PROCEDURE FOR MEASUREMENT OF INTRAOCULAR PRESSURES USING THE MENTOR TONOPEN XL

Overview:

The Mentor Tonopen XL unit is a precision electronic tonometer, which measures intraocular eye pressures (IOP). The Tonopen is easy to use and can measure IOP reliably with minimal training. It is easily portable and versatile. The accuracy of the Tonopen is equal to that of other electronic applanation tonometers. It is correlated with Goldmann applanation tonometry and other measurements of intraocular pressure.

Intraocular pressure is measured in both eyes using the Tonopen before the pupils are dilated.

### 2.6.1 Calibration check

a. The Tonopen is internally calibrated, thus the instrument calibration should be checked only before the first use each day, after changing batteries, or after depressing the RESET button.

b. If the previous calibration was good, the LCD (the small window on the Tonopen that displays messages) will briefly display "----" followed by "====" and a beep.

c. If the previous calibration was bad, then a long beep sounds, followed by "CAL" and a short beep. The display will then change to "----" and another short beep will sound.

d. Hold the Tonometer vertically with the probe tip pointing straight down.

e. Press and release the activation switch twice in rapid succession. Two beeps will sound and "CAL" will appear on the LCD.

f. Wait until a beep sounds and "UP" appears.

g. Quickly turn the Tonopen XL unit so that the probe tip is pointing straight up.

h. Wait a few seconds. A second beep will sound indicating the end of the calibration check.

i. Read the output on the LCD. If it says "Good" it was successful, if it says "bAd", calibration was not successful and you need to repeat the process.

### 2.6.2 Subject Preparation

a. Instill one drop of the Ophthetic (topical anesthetic) into the lower fornix of both eyes. Avoid contact with lashes or lid margins.

b. Position the subject in front of a fixation target (any item at eye level at least 3 ft away that the patient can look at with the eye not being tested) to minimize eye movement.

c. Place a fresh latex Ocufilm cover over the tono-tip for each subject. It is not necessary to change it testing the eyes of the same subject.

### 2.6.3 Subject Examination

a. In order to measure the eye pressure of the right eye, you need to instruct the subject to look at the fixation target with the left eye.

b. Hold the Tonopen XL as you would a pencil.

c. Position yourself to facilitate viewing of the probe tip and subject's cornea (the very front of the eye). Central corneal contact is recommended.

d. Before making contact with the cornea, activate the Tonopen XL unit by depressing the activation switch momentarily, then release.

e. The LCD will change to "====" and a beep will sound when the Tonopen XL is ready to take a measurement.

f. Once activated, touch the tip to the cornea lightly and briefly, and then withdraw. Repeat several times. The corneal surface needs to be momentarily contacted; indentation is not required and may lead to inaccurate readings.

g. A click will sound and a digital IOP measurement will be displayed each time a valid reading is obtained.

h. After four (4) quick valid readings are obtained by the tonopen, a final beep will sound and the averaged measurement will appear on the LCD along with the single bar denoting the amount of statistical error (reliability). Record the information on page 11 of the vision forms.

i. Now, measure the eye pressure for the left eye and record the information on page 11 of the vision forms.

j. Replace the Ocufilm tono-tip cover before using the Tonopen XL on another subject and before storage.

k. Do not clean the Tonopen tip. See the instructions for cleaning the Tonopen in the Tonopen Appendix.

l. If the eye pressure is equal to or greater than 30 mmHg, the subject should not be dilated. If the eye pressure is equal to or greater than 30 but less than 35 mmHg, the subject should be referred to an eye doctor within 48 hours. These subjects can have one non-dilated Canon Fundus photograph per eye. If the pressure is equal to or greater than 35 mmHg, the subject should be referred to an eye doctor within 8 hours.

m. If the eye pressure is between 24 and 30 mmHg, the subject can be dilated if there are no other exclusions. The subject should be referred to an eye doctor within one week

## ***DO NOT CHECK PRESSURE IF:***

1. Subject is not being dilated
2. Subject is allergic to Proparacaine or Tropicamide
3. Has had eye surgery within the last 2 weeks

### 2.7 PUPIL DILATION

Angle depth should be estimated with a penlight. The penlight is held several inches from the temporal limbus of the cornea with its light beam traversing horizontally across the anterior chamber of the eye. In subjects with wide-open angles, the light will be seen from the temporal limbus to the nasal limbus. If the chamber is shallow, a shadow will be cast onto the nasal iris due to the bowing forward of the lens-iris diaphragm in patients with shallow anterior chamber (van Herick W, Shaffer RN: Estimation of width of angle of anterior chamber; Incidence and significance of the narrow angle. AJO 68:624-629, 1969).

### 2.7.1 SUBJECT DILATION

For all subjects to be photographed, the pupil size is recorded for both pupils on the Eye Photo Form (page 9). If it is okay for the subject to be dilated, dilate both eyes with one drop of 1% Tropicamide. Proper placement of eye drops in the subject's eye is imperative. Note that the subject should be looking up and away from the bottle tip, that the tip does NOT touch the subject's eyelid or eye, and that the lower lid is gently held down to form a "pocket" for the drop. Make sure the subject closes their eyes after you instill the drop and practices nasolacrimal occlusion.

Adequate dilation of the pupil is desired for good quality photographs. Sufficient time should be allowed for dilation to reach at least 5mm. You may use a millimeter ruler held up near the subject's eye to determine the size of the pupil. Check pupil dilation with a penlight to make sure the pupil is not reactive to the light. If the pupil is not 5mm in diameter after 15-20 minutes, another set of drops may be instilled. If after another 15 minutes the pupil is not 5mm, the photographer should proceed with the photography portion of the exam and attempt to acquire photographs with the best possible view of the macula. The pupil size for both eyes should be recorded on the Eye Photo Form (page 9).

### 2.7.2 SUBJECT EXCLUSION

## ***DO NOT DILATE IF:***

1. Subject's eye doctor told subject to not be dilated
2. Subject is allergic to dilating drops
3. Subject refuses dilation
4. Anterior chamber appears to be narrow by penlight exam
5. Subjects with eye pressures of 30 mmHg or more.
6. If an anterior chamber interaocular lens appears to be present

# FUNDUS PHOTOGRAPHY

## 3.1 INTRODUCTION

Photographs of the retina of each eye will be taken through pharmacologically dilated pupils (unless medically contraindicated or refused). The retinal photographs will be taken with a Canon CR-45UAF 45-degree auto-focus fundus camera or a Canon CR-6 45-degree auto-focus fundus camera.

### Photography Protocols

The fundus (retinal) photography protocol is a modified version of the protocols used in the Atherosclerosis Risk in Communities Study (ARIC)- Retinal Photography Protocol.

### Photographic Guidelines

Before attempting photography, the photographer should become very familiar with the camera through a training session and by learning the terminology in the camera's operations manuals. The following protocol uses terminology from the operation manual and it is recommended that each photographer review the entire manual.

IN CASES WHERE BOTH EYES ARE DILATED, THE RIGHT EYE IS ALWAYS PHOTOGRAPHED FIRST.

Note that prior to photography, the dilated pupil measurement for each eye in mm must be recorded on the Eye Photo Form (page 9) as well as in the comments section on the Photography Log Form.

FOR SUBJECTS WHO CANNOT OR ARE NOT DILATED, PHOTOGRAPHY IS TAKEN ON THE EYE WITH THE WORST VISUAL ACUITY FIRST (the eye that reads the fewest letters on the Bailey Lovie chart during the vision testing).

For subjects who cannot be dilated or refuse dilation, the room is darkened where the Canon camera is located (about 5 lux-barely enough light to read). The subject must remain in the darkened camera room for at least 10-15 minutes. This will allow the pupils to dilate naturally. The photographer must keep lighting conditions to a minimum at all times in order to attain a larger pupil for photography. Note that prior to photography, the photographer must record which eye is photographed first and write "not dilated" in the comments section on the Photography Log Form. This process is then repeated for the other eye.

### Subject Explanation and Informed Consent

The photographer should describe the photographic procedures to the subject prior to taking photographs. Subjects are often anxious about this part of the examination, being frightened that the bright lights may cause a problem or that x-rays are used. The photographer should stress how important photography is for evaluating the retina, that the bright lights are not harmful, and that any afterimage (often associated with color changes) will fade within 5-7 minutes. .

Photography begins with a complete explanation of the procedure by the photographer. A Polaroid print may be useful to show what the optic nerve and retina looks like. It is important to reassure the subject that no retinal damage is caused by this procedure. The camera flash is bright and the subject should know when to expect a flash. The photographs will include the macula (area of central vision) and it is normal to experience a blue or red tint in the vision immediately following the flash. This disappears within five to seven minutes. Dilation drops will be used for this examination ***and the eyes will not be touched***. A sample script of a typical retinal photography explanation (suitable for use as written material for deaf or interested subjects) follows.

> **We will be taking photographs of the inside of the back (the retina) of both of your eyes so we can study whether there is any evidence of eye problems. We will not be touching your eyes, but will be giving you eye drops before we take the pictures. You will be asked to sit in a room in front of a special camera with your chin in a chin rest. We darken the room so we can align and focus the camera. During the aligning process, you will only be aware of some small red or green lights, which may be visible in the camera lens. We will ask you to follow the lights. Just before we take the picture, we will ask you to blink your eyes and then open them real wide. When we photograph the retina, the camera will flash a bright flash from within the camera lens.**
>
> **Sometimes, just after this picture is taken, you may see a blue or red circular spot. This will disappear within 5-7 minutes and causes no permanent damage to the eye. Please remember that we are only taking pictures (not x-rays) of a small portion of your eyes and a picture of your whole outside eye and that these pictures will not substitute as an eye examination. You will certainly be notified should we notice anything requiring immediate attention. Please continue to see your eye doctor on a regular basis for your complete eye examinations.**

## Examination Protocol

### Subject ID Numbering

**It is crucial to the study that all photographers become thoroughly familiar with the subject ID numbering system that will be used to identify all of the photos taken.**

All subjects are assigned an ID number that is consistent with the numbering system used in the SOF study. This consists of a five-digit sequence. The first **non-zero digit** indicates the site as follows:

Baltimore = 1 Minneapolis = 2 Pittsburgh = 3 Portland = 4

The next four digits are the subject's number. The ID number of an individual consists of the site number followed by the individual's number. Individual subjects are numbered from 0001 to approximately 1500 (depending on enrollment per site).

For example, ID number 040010 identifies subject number 10 from Portland, whereas ID number 21245 identifies subject number 1245 from Minneapolis.

### Photography with Poor Fixation

The photographer will attempt photography on subjects with poor fixation. These subjects may be unable to direct their gaze so that their optic nerve is properly positioned on the field alignment template located on the camera monitor (as may be the case where both eyes are blind or when the subject is deaf and communication with her is impossible). In such cases, the photographer should attempt the best field definition possible. Remember that it is best to position the macula in the center of the field alignment template because we are most interested in the macula.

The photographer should attempt photography on those subjects who are physically disabled, if they can be comfortably positioned at the camera. To facilitate this, the subject may remain in a wheel chair positioned before the motorized camera table, which can be lowered to the appropriate height. Care should be taken when lowering the camera table to avoid pressing against the subject's legs. If the subject cannot be comfortably positioned, no photography will be performed. This should be noted on the Eye Photo Form (page 9).

## 3.2 SUPPLIES

The following supplies will be provided to you by the UCLA Coordinating Center:

- Film
- Proparacaine 0.5% eye drops
- Tropicamide 1.0% eye drops
- Rev. Eyes 0.5 eye drops
- 100% Cotton
- Lens cleaning fluid (100% alcohol)
- Kleenex tissues
- Alcohol wipes
- Spare view bulbs
- Fuses for electrical circuits
- Film roll processing labels (1" by 2")
- Varta 2CR5, lithium 6-volt batteries for 35 mm Canon camera body
- Contact lens holder and saline solution
- Paper tape
- Sharpie markers (black, fine point)

Disposable penlights
Mydriatic glasses

## 3.3 EQUIPMENT SET UP

The camera dust cover and lens cap should be removed at the beginning of the day and the lens inspected and cleaned as necessary. **Dust is the greatest enemy,** producing the majority of artifacts on the photographs. **When the camera is not in use, the lens cap should be in place and the special dust cover must remain on the camera.** The 35 mm camera and the camera back should be checked for sufficient battery power, and the film counter should be checked to be certain that the camera is loaded with adequate film before beginning photography. Please do not allow smoking in the rooms near the camera.

## 3.4 RETINAL PHOTOGRAPHY

### Introduction to Retinal Photography

As part of the ophthalmic photography component, two retinal photos of each eye and one external (eye reference) photo of each eye will be taken.

### The Canon CR-45 UAF or CR-6 Camera

A Canon non-mydriatic, auto-focus fundus camera with a 35 mm camera back will be used for the photography section of the eye exam. The camera is mounted on a motorized instrument table to allow optimum alignment. Both photographer and subjects have pneumatically adjustable stools, the latter with a backrest and floor lock mechanism. Aside from the template for right and left optic nerve placement that has been superimposed on the viewing screen, there are no other modifications made to the Canon CR-45UAF or the CR-6 camera.

The video display is activated when the power switch on the side of the main unit is turned on. If no photography or switch operations are performed for 10 minutes, a power saving mode is activated, turning the lamps and display off to prevent unnecessary wear. During this power saving mode a "ready" lamp blinks on the monitor. Pressing any button below the arrows under the monitor, the joystick trigger, or the alignment button will reactivate the system.

Notice that three vertical arrows blink on the monitor when the main unit is switched on. This indicates the system is charging up. **Do not take photographs until the blinking stops, indicating a fully charged flash. Pictures taken before the flash is fully charged will be severely underexposed.** The current date and subject ID number are displayed in the upper left-hand corner of the monitor. The camera contains an internal clock and the date will automatically change each day. The photographer must manually change the date if this clock should fail or if the camera is left unplugged for a long period of

time. The date and time display is changed through Menu 3. The date format will read Month-Day-Year. The "Time Set" screen is used to adjust the current date and correct time. The camera is capable of recording up to a five-digit ID number, accessed through Menu 3, which ***must be reset for each subject photographed***. Once properly entered into the camera, the number will appear below the date on the monitor. ***This number must be checked and adjusted before each subject is photographed because this information is recorded on each slide and will become a permanent part of the data slides and will become the primary identifier for each picture. At the same time that each photo is taken an entry must be made in the Eye Photo Form (p. 9) and in the Photography Film Log.***

The 35 mm camera body should be attached to the main unit and loaded with the film provided to you from the Central Coordinating Center. The photographer needs to check that film is loaded in the camera at the beginning of each photography session. To load the film, open the camera by sliding the camera latch down while pressing in on the cover lock button. Insert the new film cartridge in the left side and thread the film across the shutter to the right side, making sure that the film leader is aligned with the orange index mark. Be careful not to poke the shutter blades with a finger because damage to the blades can easily occur. Take up any slack in the film by sliding excess film back into the cartridge. Close the back; the camera automatically threads the film and advances the film and counter to the number one exposure position. A blinking "check film back" warning on the monitor or blinking film marks on the camera back LCD display indicates the film is not loaded properly. In this case, reload the film. When the film is properly loaded, the camera back "reads" the film speed and automatically adjusts the flash output. At this point the photographer must press the "DSP" (display) button below the monitor to confirm that the following settings are correct:

| | | |
|---|---|---|
| Back: | **RE 100 45** | (35 mm EOS body, 100 ASA, 45 degree field) |
| AF: | **ON** | (autofocus on) |
| AE: | **ON** | (autoexposure on) |
| BLIN: | **ON** | (blink detector on) |
| K: | | |
| SPLIT: | **IN** | (split focus detector in) |
| NO: | **H 030001** | (SOF Eye Study Subject ID #)* |
| DATE: | **MM-DD-YY** | (correct date and time |
| | **12:00** | |

* The "H" before the subject ID number stands for "HOLD" (i.e. the camera holds the same number until it is changed for another participant). The frame counter on the top of the camera will indicate the number of exposures taken. After 36 pictures are taken, the camera automatically rewinds the film. If the film

needs to be removed before 36 exposures have been taken, a manual rewind button on the 35 mm camera back needs to be depressed.

### Pupil Size and Alignment

The alignment switch is turned on, which displays the pupil alignment template on the video monitor of the camera. This template consists of a center circle measuring 4 mm in diameter and an outer circle, which is 9 mm in diameter. The camera base is moved to center the pupil in the center circle. The pupil should coincide with the center circle on the monitor when it is positioned properly. Make sure that if the eyelids do not open all the way, you consider holding or taping the eyes open. The camera joystick is moved forwards or backwards until the pupil appears perfectly round. At this point, proper external alignment has been achieved. A pupil larger than the central 4 mm circle on the monitor is required for adequate fundus photography. Even if the eye doesn't dilate to at least 4 mm, the photographer should attempt to still photograph the macula.

### Internal Eye Alignment

Once proper external pupil alignment is achieved, the alignment switch is pressed to provide a view of the fundus, split focusing lines, corneal reflection dots, and the fixation light. If no split focusing lines are seen, the height or left/right adjustment is improper, the "SPLT" (split lines) setting is set to "OUT" (Menu 1), or the diopter compensating slider is pulled out. The split lines may fade in and out if the pupil is too small, the alignment of the camera is not centered on the pupil, or if the eyelashes or lids eclipse the light. If no corneal reflection dots are seen, the forward/backward adjustment is improper. ***The best photographs are obtained when the eye is well dilated, fixated on the target, and lids and lashes are held wide open.***

### Focus with High Myopia (Near-sightedness, over –12.00 diopters of correction) or, Hyperopia (Far-sightedness, over +15.00 diopters of correction).

The diopter compensation slide should be set to the "0" position. This is the only setting in which the auto-focus mechanism works and allows photography of eyes with refractions between –12 and +15 diopters. In the event that the eye photographed falls outside this range and auto-focus cannot be achieved, as in the case of aphakia (where a subject has had the lens removed) or high myopia, the diopter compensation slider must be adjusted for the clearest focus to the "+" or "-" position and the focusing knob is then turned manually to provide the sharpest image on the monitor. This is facilitated by obtaining a brighter retinal image on the monitor by increasing the view light intensity. The normal setting for the view light intensity adjustment is approximately 4. Remember that the camera is now in manual focus rather than auto focus. For instructions on manually focusing the Canon camera, see "Focusing Manually When the Auto-Focus Mechanism Doesn't Lock" below. Standard monitor functions can be adjusted for the photographer's viewing comfort (including contrast and brightness) by opening the access door below the

monitor. These are standard controls similar to those found on any TV monitor and only affect viewing; they do not affect final photo quality.

### Alignment, Focus and Proper Fixation

While viewing the fundus image on the screen, the photographer adjusts the internal fixation light while instructing the patient to look at the blinking green light visible in the camera lens. The subject should view the target with the eye being photographed. **To facilitate consistent positioning of the macula, the camera monitor will have a transparent overlay added indicating the proper optic nerve position for right and left eyes.** In the absence of this overlay, the optic nerve should be positioned two disc diameters from the nasal edge of the camera frame and should be centered on an imaginary horizontal line bisecting the camera monitor. When the auto-focus mechanism focuses the camera on the retina, a motor adjusts the focus knob until the auto-focus "locks" and a clear image is identified. This "lock" is confirmed in two ways. Two vertically stacked equal signs appear in the lower left-hand corner of the screen. Also, two rectangular boxes appear, stacked one on top of the other, in the center of the monitor.

### Focusing Manually When the Auto-Focus Mechanism Doesn't Lock

If the operator notices that the auto-focus mechanism can't "lock" (obvious when the motor keeps running for several seconds and then shuts off) or if the mechanism "locks" without stacking the vertical boxes, the photographer should manually focus the camera by turning the focus knob until the two rectangular boxes in the middle of the monitor appear stacked. This method of assisting the auto-focus mechanism will help assure the most accurate focus possible.

### Camera Positioning

Once the fixation is confirmed, the photographer must **constantly** adjust and position the camera to maintain the correct position of the corneal reflection dots. **It is important that these dots be properly positioned at the 3:00 and 9:00 positions before the picture is taken.** This will ensure the correct distance from the eye and will allow a sharp image to be produced on the film. Focus is done automatically, but should be confirmed by the photographer by assessing image sharpness and by checking the auto-focus confirmation indicator on the monitor.

The photographer will instruct the subject to blink once or twice just before the picture is taken. This blinking will insure a moist (and subsequently clearer) cornea and will safeguard against unwanted blinks at the moment of exposure. Once alignment is satisfactory, the shutter release, located in the tip of the joystick, is depressed and the exposure is made.

### Sequence of Retinal Photos

***Two retinal exposures will be made for each eye of all subjects.*** Following the first N (normal) exposure, another exposure will be made. The photographer will press the "RE-N" button under the main screen until a "+" appears in place of the "N" thus indicating a 1/3 f-stop ***increase*** in exposure.

### External Whole Eye Photo

***Following the retinal photos, each eye will also have an external whole eye ( eye reference) photo taken.***

The camera is pulled back toward the operator, and the compensating lens slider is moved to display an "a". The photographer ***focuses the camera manually on the iris***, sets the exposure to "N", frames the eye with the lens at the center, and takes the photo.

**Then three similar photographs of the other eye will be obtained. Thus each eye will have two retinal photographs and one external photograph. One of the retinal photos will be at "N" and one at "+" (a 1/3 f=stop increase in exposure). The external photo will always be exposed at "N".**

### Retake Policy

Should the photographer suspect that an inadequate photograph was taken (due to a possible shadow, excessive movement or misalignment, or should the subject comment that they did not see the flash), a second picture at that exposure (N or +) should be taken.

### Retakes When the Subject is Not Last on the Film Roll

When retakes are present on a roll of film, and the subject is the first through the fifth, the photographer must unload the roll from the camera following the end of the particular subject's sequence of photos, even though the roll is not used completely. To unload film, when the roll is not used completely, the photographer must depress and hold down the manual rewind button for over two seconds. The camera then rewinds the film automatically. When this occurs, a note must be made in the comments section of the Photography Log Form indicating the circumstances, as well as, the eye and the number of retakes done.

### Retakes When the Subject is Last ($6^{th}$) on the Film Roll

If the subject is the last ($6^{th}$) on the roll of film, a new roll of film must be loaded into the camera in order to complete the sequence. The photographer must unload the retakes on the new roll of film following the last photo of the subject that is taken, even though there will be unused film remaining. When this occurs, a note must be made in the comments section of the Photography Log Form indicating the circumstances, as well as, the eye and the number of retakes.

## 3.5 REVERSAL OF DILATION AND SUBJECT REFERRAL

One drop of Daprizolamide is to be instilled into each eye after the photography session is completed. Since the dilation may take an hour to be reversed, the subject should be offered the use of temporary sunshields or sunglasses. They should be instructed not to drive for several hours.

## 3.6 FILM: HANDLING, SHIPPING, AND LOGS AND RECORDS

### Film Concerns

All films must be stored at a temperature of 55 degrees Fahrenheit or lower. A conventional refrigerator is the perfect storage container for the Professional Ektachrome. Please remove the film from refrigeration at least 1 hour (but no more than 24 hours) to allow it to warm to room temperature before use. This warming is necessary to prevent condensation inside the camera or film tearing, which can occur when the film is cold. You may also freeze this film if refrigerator space is at a premium. In this case, please be sure to remove any rolls at least 3 hours before use to allow ample time for the film to reach room temperature. Any film warming to room temperature must be left in its plastic storage container to prevent condensation. Do not refrigerate the film after exposure. Film should be sent to Colleen Gillis at Advanced Vision once a week on a Monday, Tuesday, or Wednesday.

### Film Tracking and Numbering

Once film is exposed and unloaded, a numbered film roll label is attached to the exposed roll. The number on the film roll must correspond with the roll number listed on the Photography Log Form. The marking system on the label will consist of the date that the film was loaded into the camera and the following alphanumeric code as show below:

Date loaded
Center number- roll number.

For example:

**Feb 05 00**
**1-023**

Roll number 23 was loaded at the Baltimore site on 02-05-00.

**Jun 17 00**
**4-206**

Roll number 206 was loaded at the Portland site on 06-17-00.

**Photography Log Form**

The photographer will keep a log of all study subjects that are photographed (Photography Log Form). This form includes: Subject ID number, date of photography, photographer ID number, eye photographed, a comments section, and the film roll number. The photographer will keep the original of these forms. Xerox copies of the forms accompany the corresponding rolls of film when shipped for processing.
Comments on any special circumstances, such as excessive subject blinking, or concerns about retinal pathology are encouraged and can be recorded in the comments section on the form. This information will be helpful in understanding any artifacts that may appear on the processed slides. This information will be taken into consideration when Ms. Gillis provides feedback to the photographers.

The film rolls will be numbered consecutively beginning at each site with roll number one and advancing to the next numerical digit as a new roll of film is used. Once a roll is exposed, it is removed from the camera and the canister is marked with the number listed on the corresponding Photography Log Form.

**Film Sequencing**

We will be taking 6 photos per subject. Therefore the camera will need a new roll of film after every six subjects are photographed.

**Film Shipping**

After checking that the roll of film has been correctly identified, it is important to ship it together with a xeroxed copy of the Photography Log Form. Exposed film rolls will be sent to Ms. Gillis weekly. If a roll of film is not completely exposed, it should be sent to Ms. Gillis after three weeks from loading it in the camera. Film will be sent to Ms. Gillis at Advanced Vision via Federal Express~~-~~, Airborne or any other express carrier weekly VIA 2$^{ND}$ DAY DELIVERY on Mondays, Tuesdays or Wednesdays, BUT NEVER on Thursdays or Fridays or the day before a holiday. The photographer must attach a numbered film roll label to each exposed roll of film before sending it to Ms. Gillis. The film roll number must correspond with the sequential number appearing on the corresponding Photography Log Form.

The following shipping label example contains the correct address to be used for all photographic shipments sent to Ms. Gillis.

Ms. Colleen Gillis (SOF-AMD)
Advanced Vision
2100 W. State Road 434, Suite 1020
Longwood, FL 32799
Phone: 407-389-0800

## 3.7 RETINAL PHOTOGRAPHY AND THE CARE AND MAINTENANCE OF THE CANON CR-45 OR CR-6 CAMERA

### Care and Maintenance of the Canon CR-45UAF or CR-6 Camera

The retinal camera should remain covered when not in use. ***High humidity or temperatures must be avoided.*** Dusty conditions mean that the camera will need frequent cleaning. The objective lens should be checked and cleaned with the air bulb if necessary ***before each subject is photographed.*** A more extensive cleaning is required to remove grease, smudges, or stubborn spots from the lens. This cleaning requires removal of the lens "boot" and external alignment lamp ring and should be referred to the primary photographer at each clinical center.

### Lens and Camera Body Care

Before each photograph, the camera lens must be inspected and, if dirty, cleaned with the brush and air bulb to remove debris. Should more extensive cleaning of the lens be required, the lens can be fogged with your breath or moistened with absolute alcohol and then wipe gently using a circular, polishing motion with the 100% cotton until no dirt or oily film is visible on the lens when it is viewed from the front ***with the alignment lens removed and the view lamp on and turned up to its maximum intensity.*** The body of the camera should be kept cleaned and free of dirt with a soft cloth and water or a common spray cleaner. The headrest may be cleaned with alcohol. The inside of the 35 mm camera back should be inspected for dirt and film fragments ***each time the film is changed.*** The air bulb or a puff of air is used to clean inside the camera back. The infrared mirror relay lens assembly is cleaned as necessary to remove dirt or dust when seen on the display monitor. While these specks do not affect final photo quality, they are distracting and should be removed. ***Never touch, brush, or puff air onto the mirror that is located at the front of the 35 mm body.***

### Instrument Table and Stools

The instrument table and stools can be kept clean by wiping with a common spray cleaner and a soft cloth. A drop of WD 40 may be used occasionally on the caster on the table and stools. The electric

motor on the table requires no lubrication. The motor is protected by fuses that may need replacing should they be damaged by excessive current.

### Flash and View Lamp Concerns

It is anticipated that the flash, and view lamps will fail at some point. Remember to keep all oil from your fingers off these lamps during replacement. The view lamp should last approximately one to two years and is easily replaced as needed. The flash lamp has a life of at least 5,000 flashes, enough to complete the study. Since the view lamps are relatively inexpensive bulbs, one spare should be ordered from Canon and kept at the clinical center. The flash lamp is expensive and can be ordered by overnight delivery, if needed, from Canon.

As the flash lamp ages, the light output can gradually diminish, producing progressively darker photographs. This can temporarily be over-ridden by an adjustment of the transformer output, although ultimately the lamp should be replaced. The decision to replace the lamp, due to dark photos will be made with the UCLA Senior Photograph following routine review of processed photographs. ***The flash lamp requires careful handling during installation (the burned out lamp may be hot and the new lamp must be properly aligned). Thus, replacement should be attempted only by clinical center staff who have been trained to do this.***

### Camera Malfunctions and Errors

Since the camera requires virtually no other maintenance, any malfunction will need to be investigated first by the photographers at each center and, when necessary, via telephone with the Senior Photographer, Colleen Gillis. Trouble-shooting can be performed via telephone to diagnose any malfunction. Some camera malfunctions or photographer errors are not evident during photography and will only be discovered after examination of the processed films by Ms. Gillis. This includes camera flash synchronization, transformer power settings, and problems with a dirty objective lens or film loading problems. For this reason, prompt shipping of the film to Ms. Gillis is essential. Steady communication between the photographers and Ms.Gillis is imperative should a problem or concern arise. If a malfunction is discovered during photography or the photographer has a problem or question needing immediate attention, Ms. Gillis is available via pager (877) 466-0073.

Service information can also be obtained directly from Canon USA. Our contact person at Canon Medical Systems is Gary Rackler, Technical Support Specialist (972) 409-8872 (grackler@cusa.canon.com).

### Photographer Certification

Each photographer will need to become certified before taking photographs of study subjects. Training will be provided initially in a group setting where the photographers will receive didactic and hands-on

training. Following the training session, photographers will continue to practice what they learned on the Canon camera in order to submit photographs for provisional certification. To become provisionally certified, photographers must submit photographs of ten eyes of non-study subjects to Ms. Gillis. Of the twenty photographs submitted, a minimum of four should be photographed on volunteers who are 75 years or older.

Photographers whose photographs are consistently of good quality (overall grade of good or fair in at least 75% of a series of 10 eyes of study subjects) will become fully certified. If photographic quality for a fully certified photographer falls below this criterion, certification will revert to provisional status and special attention will be aimed at improving the quality of the work. In order to retain familiarity with equipment, technique and protocol, it is crucial that the back-up photographer participates and takes photographs on at least one subject per week.

Because additional personnel may need training to become certified, it is acceptable for a certified photographer at that clinical site to provide instructions. The trainee will then prepare and submit photographs to Ms. Gillis for provisional certification.

# HOME EXAMINATION

The home examination consists of two parts: Ocular History and Visual Acuity.

## 4.1 Subject Identification & History

The subject's SOF record number, date of birth, date of examination and place of examination will be filled in when the subject is first registered for the eye examination. Under the place of examination; 1 = "clinic" refers to examining rooms, 2 = "local" refers to any exam done by the SOF staff outside the "clinic", e.g., in the examinee's home, nursing home, hospital, etc.
In all exams, the right eye will be evaluated first. Prior to beginning the exam, the examiner will determine the status of both eyes by asking the following questions:

Vision Interview

1. At present time, would say your eyesight (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor, or are you completely blind?
2. How much of the time do you worry about your eyesight?
3. Are you currently using eye drops in your eyes for any reason?
4. Have you ever used eye drops prescribed by a doctor to lower the pressure in your eyes?
5. Have you ever been hit in the eye with a fist or an object?

The next questions are about how much difficulty, if any, you have doing certain activities while wearing your glasses or contact lenses, if you use them for this activity.

6. How much difficulty do you have reading ordinary print in newspapers?
7. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools?
8. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs, in dim light or at night?
9. How much difficulty do you have driving during the daytime in familiar places?
10. Are you limited in how long you can work or do other daily activities such as housework, child care, school, or community activities because of your vision?
11. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
12. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

Ocular History

1. Has a doctor ever told you that you had any of the following?
    a. Cataracts?
    a1.Cataract extraction (surgery)?
    a2. Combined cataract/glaucoma surgery?
    a3. If YES to b or c, during cataract surgery was a new lens placed in your eye?

a4. Yag capsulotomy or treatment for 2nd cataract in the same eye?

b. Glaucoma?
c. Macular degeneration?
d. Uveitis (inflammation of the eye)?
e. Stroke of hemorrhage of the eyes?
f. Diabetes in the eyes?
g. Blind eye?

2. Have you ever had eye surgery or laser treatment other than cataract surgery?
   a. Laser surgery for diabetes?
   b. Laser surgery or photodynamic therapy or other procedures for macular degeneration?
   c. Glaucoma surgery, including laser surgery for glaucoma?
   d. Retina surgery?
   e. Corneal graft or transplant?
   f. Refractive surgery (a procedure that allows you to not wear glasses, or to wear less powerful ones)?
   g. Enucleation (removal of eye)?
   h. Other eye surgery?

Please be sure to return to the Vision Checklist (Page 1 of the forms) and mark your rating of the ocular history and any comments you feel are relevant.

## 4.2 Visual Acuity Testing Using A Portable Eyetest Case (Good-Lite Box)

a. Illumination: The portable eye test case is illuminated, so abrupt changes in illumination should not be a problem.

b. Distance: The test is administered with the subject seated at 10 feet from the eyetest case. Measure from the eyetest case to the middle of the chair using a metal tape measure.

c. Glasses: Acuity is tested with habitual correction for distance vision.

Before testing vision, ask the subject if she normally wears glasses, or contact lenses, or both for distance vision. (Probes: "Do you wear glasses to see things far away, like when you go to a movie theater or when you drive a car?") If she answers that she has glasses for distance but sees better without them, distance tests should be performed with her wearing her glasses (her "Best-corrected" state). If she wears eyeglasses, please identify if she wears distance only, bifocals, or no line bifocals (trifocals, progressives, or any multifocal eyeglasses will be marked as "bifocals," or "no line bifocals" on the form [p. 17]).

### Equipment

a. Occluder

b. Illuminated eye chart- Good Lite Box, with "SLOAN" chart for 10 feet.

| | |
|---|---|
| 20/100 | KHOR |
| 20/80 | CKZDV |
| 20/60 | OZNRHVC |
| 20/50 | RKCSZHVD |
| 20/40 | SDKH ORCV |
| 20/30 | HOCZR KDSVN |
| 20/25 | NZCOS KDVRH |
| 20/20 | DCSKO VRNHZ |
| 20/15 | ZSVDK HNORC |

The Sloan Chart for ten feet will show the above configuration of letters.

**Measurement Procedures**

a. The portable eye test case should be placed at approximately the eye level of seated subjects. Ten feet from the midline of the body to the chart seat subject on straight-backed chair.

b. Ask the subject to hold the occluder so that her left eye's vision is blocked and only the right eye can be tested. Then ask the subject to start reading the letters on the chart starting with the 20/50 line and proceed down the chart toward the smaller letters. Say:

"I'd like you to read aloud the letters on this chart. Read from left to right.

Don't squint and don't lean forward. Start at the top row and read down as far as you can."

If she reads it with less than 3 errors, say "Now, can you easily read the next row?" "OK continue." Continue until she makes 3 or more errors in a row.

If she says no or reads it with three or more errors, then say: "Please read the top row."

If she cannot read the top row or makes 3 or more errors, then you need to test at 5 feet (low vision distance) using the same procedure. Be sure to record that you are testing at 5 feet, on form p. 17.

c. As the subject reads, mark the letters by drawing a line over those read correctly and drawing a line through the incorrect ones.

d. When it is apparent that the subject is struggling (e.g. misses 3 letters on a row or goes very slowly) stop.

Note the errors on that row. If she misses three of the letters on a row, use the previous row as the Snellen Acuity score. If she says, "That's all," in the middle of a row, have her guess at the rest of the row and then stop. Draw a line through the first row not attempted.

Be watchful for participants who inadvertently "peek" out from under the eye paddle. They may have their best eye covered and unintentionally will move the paddle over a bit in order to see better. Move the eye paddle into the proper position on the subject's face. You may even need to hold it in place for some patients or add a tissue behind their eye glasses to cover the eye not being tested.

If the subject is trying to read too quickly, be sure to slow her down. Ask her to take her time and read each letter carefully.

e. REMEMBER TO RECORD THE NUMBER OF LETTERS READ CORRECTLY AND THE CHART DISTANCE.

f. For subjects that cannot see the chart at 5 feet, you need to test their vision with your fingers. Finger counting is tested by holding two or three fingers two feet from the patient and should be recorded as 96. Hand motions is tested by moving a hand back and forth in front of the patient with the other eye occluded. This is recorded as 97. Light perception is tested by carefully occluding the fellow eye and directing the light of the penlight at the examinee's eye from about one-foot distance. This is recorded as 98. No light perception is recorded as 99 on page 17.

g. The subject now holds the occluder so that the vision from the right eye is blocked. Steps b-f are repeated for the left eye.

# Reasons for Referral to an Ophthalmologist or Eye Doctor

**Subjects to be referred to an Ophthalmologist Within 8 Hours**

Subjects with eye pain and redness that is not relieved with blinking or with artificial tears.
Subjects that see new halos around lights.
Subjects that become nauseated and vomit.
Subjects that complain of itchy, red, and swollen eyelids.
Subjects that have eye pressures equal to or greater than 35 mm Hg.

**Subjects to referred to an Ophthalmologist within 48 hours**

Subjects that have eye pressures equal to or greater than 30mm Hg and less than or equal to 34 mm Hg.

**Subjects to be referred to an Ophthalmologist within One Week**

Any subject with eye pressures between 24 mm Hg and 30 mm Hg.

**SOF-AMD—Photography Log Form**
**Page 1 of 2. FILM ROLL NO._____**

| | Date | Tech ID No. | Subject ID No. | Eye | Comments |
|---|---|---|---|---|---|
| **1** | | | | | |
| **2** | | | | | |
| **3** | | | | | |
| **4** | | | | | |
| **5** | | | | | |
| **6** | | | | | |
| **7** | | | | | |
| **8** | | | | | |
| **9** | | | | | |
| **10** | | | | | |
| **11** | | | | | |
| **12** | | | | | |
| **13** | | | | | |
| **14** | | | | | |
| **15** | | | | | |
| **16** | | | | | |
| **17** | | | | | |
| **18** | | | | | |

**SOF-AMD—Photography Log Form**
**Page 2 of 2. FILM ROLL NO._____**

| | Date | Tech ID No. | Subject ID No. | Eye | Comments |
|---|---|---|---|---|---|
| **19** | | | | | |
| **20** | | | | | |
| **21** | | | | | |
| **22** | | | | | |
| **23** | | | | | |
| **24** | | | | | |
| **25** | | | | | |
| **26** | | | | | |
| **27** | | | | | |
| **28** | | | | | |
| **29** | | | | | |
| **30** | | | | | |
| **31** | | | | | |
| **32** | | | | | |
| **33** | | | | | |
| **34** | | | | | |
| **35** | | | | | |
| **36** | | | | | |

## Reading Center

The SOF Photographic Reading Center (PRC) is located in the Department of Ophthalmology in the School of Medicine at the University of California, Los Angeles.

### 7.1 Other Resources for the Photography Center:

General Assistance with Canon Cameras:

Gary Rackler
Technical Support Specialist
Canon Medical Systems

Telephone: (972) 409-8872

Email: grackler@cusa.canon.com

Film purchasing from Unique Photo:

Alan Bergson
Address:

Telephone: 800-631-0300
Unique Photo
11 Vreeland Road
Florham Park, New Jersey 07932-0979

Film Processing from Photobition Orlando:

Tim Hoover
Address:

Telephone: 800-330-3578
407-660-0606
Photobition Orlando
505 Lake Destiny Drive
Orlando, FL 32810

Slide storage pages from Adorama:

Sales
Address:

Telephone: 800-223-2500
Adorama
42 West 18th Street
New York, NY 10011

### 7.2 Film Handling at the Clinical Sites Prior to Shipping to UCLA:

Film Processing:

Film will be sent to the Ms. Gillis via Federal Express weekly from the clinical sites. Even if the film does not have 6 subjects on it, it will be sent after 3 weeks for development. Partially exposed rolls of film may be removed after rewinding the film automatically by depressing the Manual Rewind Button. The photographer will attach a numbered film roll label to each exposed roll of film before sending it to Ms. Gillis. The film roll label appears as follows:

SOF- AMD
Date loaded:_____
Center #_____
Roll #:_____

The film roll number MUST correspond with the sequential number appearing on the corresponding Photography Film Log page. It is critical that a xeroxed copy of the appropriate pages from the Photography Film Log accompany each roll of film.

## 7.3 Preparing the Rolls of Film for Processing by Colleen Gillis at Advanced Vision in Florida:

1. The undeveloped rolls of film arrive at Advanced Vision in Fed- Ex envelopes. The photographer will unpack and store these rolls as a group for the next processing batch. Batches will be done two to three times a week.

2. Film logs are hole-punched if necessary. The log sheets are dated with the date received at the top of the page. Each film log is faxed to Ms. Gonzalez at 310-206-7773. These logs will be entered into a database created by Dr. Yu and Ms. Zhou.

3. Ms. Gillis will confirm that each roll of film has the appropriate label that corresponds to the Photography Log Sheet included in the Fed-Ex package.

4. When all the canisters and corresponding Log Sheets are confirmed, the canisters are then placed in a Photobition processing bag. Along with the canisters, Ms. Gillis will include an instruction sheet with appropriate directions for mounting the fundus photos. In addition, **2 prepaid coupons for each canister of film** or the billing information will be placed in the bag.

5. The bag is sealed tightly to help prevent loss of inserted materials. The package is then ready to be delivered to Photobition Orlando, which Ms. Gillis or her assistant will do.

6. Ms. Gillis will have the film processed within one day so that the results can be reviewed as soon as possible for possible camera malfunctions.

## 7.4 Pick-up of Photographs: By Ms. Gillis or her Assistant at Advanced Vision in Florida

1. Check for processed film at Photobition Orlando. A previous batch of film will be ready for pick-up when dropping off a batch to go out.

2. Unpack the boxes of slides carefully because the lid of the boxes might be loose.

3. Look for unexposed rolls or slide boxes that are not complete, which indicates camera/operator problems. If these are present, examine them and determine what caused the problem(s).

4. Talk to the Photographer at the clinical site as soon as possible and discuss the issue. Will notify the Project Coordinator and PI of any photographer or camera problems immediately.

5. Quality grading of the retinal images and entry of the data into the Access database by Ms. Gillis will be done within 2-3 working days from her picking up the processed film. Clinical sites and the PI will be notified of camera/operator problems.

## READING CENTER-PHOTOGRAPHER COMMUNICATION

Weekly, the Senior Photographer will review the quality of each photographer's work with the Program Director and PI at UCLA. The Senior Photographer or Program Director will then call the site photographers by telephone to discuss any significant problems observed. This contact will also allow the site photographers an opportunity to ask questions or make comments.

When substantial problems are observed (particularly if a photographer has reverted from full to provisional certification), the Senior Photographer will phone the photographer more frequently and update the Program Director on the progress being made to improve the photographer's quality. If the problems cannot be adequately addressed by telephone, the Senior Photographer may arrange to conduct a special photographic site visit for the purpose of observing the photographer at work and demonstrating the desired technique.

Monthly, the UCLA Reading Center and senior photographer will issue a newsletter for study technicians, regarding issues of particular interest to them and discussing methods for obtaining the most optimum results in data collection. Comparisons of dilation rates and quality of fundus images will be made.

## 7.5 Sorting of Photographs

A light box and a viewer are necessary to examine and sort the photographs. Recommended are the Logan Model 1055 slide sorters and a Larson Viewer designed for examining slides. The magnification of the loupe can range between 4X and 8X. Any lower magnification will not allow adequate visualization of retinal features; higher magnification does not allow appreciation of the "gestalt" of the picture, and magnifies the graininess of the film.

## 7.6 Labeling of Slides at UCLA

Each mount is identified on the bottom of the cardboard frame with a label on which is written or printed the subject identification number, the eye (OD or OS), the date of the visit, and the photographer's personal identification number. (AVERY laser labels #5267, ½" x 1-¾", 80 labels/sheet, 25 sheets/package) fit perfectly on the slide mounts. These labels are produced for each subject visit from the log sheets faxed to UCLA. Another copy of the log sheet will be provided to the Coordinating Center along with the slides when the slides are shipped by Fed-Ex to UCLA by Ms. Gillis.

All of the slide labels will be formatted as follows:

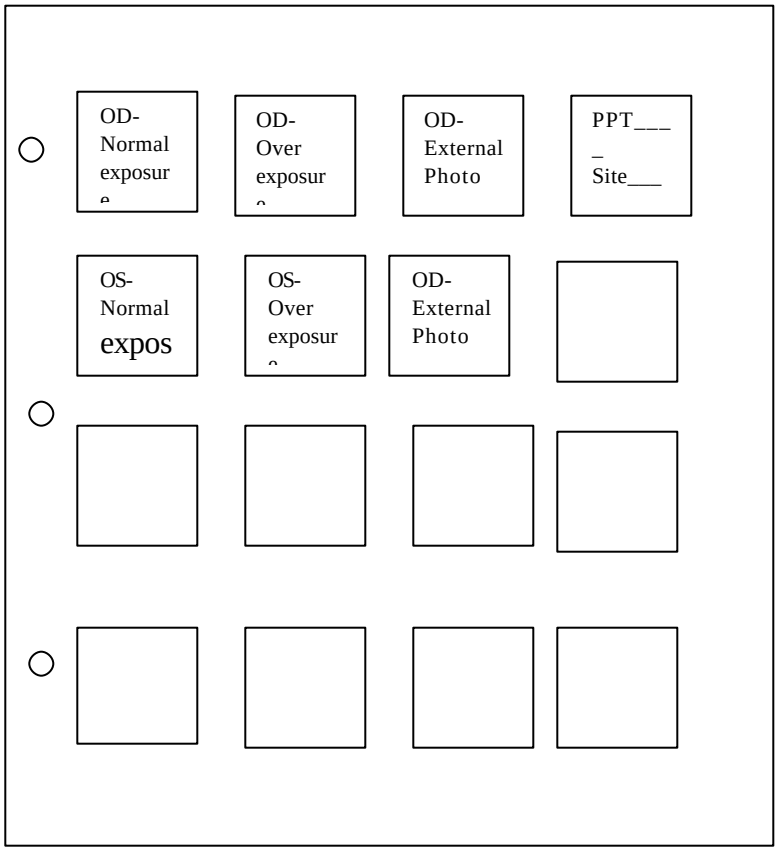
Each label will have the subject identification number, the eye (OD or OS), the date of the visit, and the photographer's personal identification number as shown below:

| | |
|---|---|
| PPT: (ID Number) OD | PPT: (ID Number) OS |
| MM/DD/YY | MM/DD/YY |
| EX: (i.e. 272) | EX: (i.e. 272) |

## 7.7 Preparation of Slides for Grading at UCLA

The mounted and labeled transparencies are placed in 9" X 11" **TRANSPARENT** plastic sheets containing 20 pockets per sheet. The plastic sheets should be constructed so that the pockets **open at the side** rather than at the top. The open side of the left pocket should face the open side of the right pocket. There is less chance of loss when the transparencies are mounted in this manner because they tend to press against each other and thus are held in place. **Please do not use frosted plastic pages.** Thin archival plastics are discouraged since they collapse on the inclined light tables used for grading. The Reading Center recommends slide pages from Adorama at 42 West 18th Street, New York City, NY, 10011, Telephone: 800-223-2500.

One plastic sheet (sleeve) should be used for each subject for each visit (1 sleeve per visit). The transparencies should be mounted so that the pocket openings face to the front facing the person mounting the slides, and the edge with the three holes for a ring binder should be to the left of the mounted slides. The transparencies should be oriented for viewing in the arrangement diagrammed below.




Each page is labeled with a slide page identification label, as below, measuring 1 ¼ by 1 ¾ inch (Avery laser label #2028) containing the clinic name and subject identification number.

Ms. Gonzalez will prepare stacks of 20 sleeves for each grader. The images of a subject from visit 6 and visit 8 will not be in the same stack. In addition, Ms. Gonzalez will ensure that images of a subject from the 2 visits are not included in the same grading batch. Ms. Gillis will do 3 stacks of 20 a week (total of 60 sleeves) and Dr. Kratz will also do 3 a week (total of 60 sleeves).

## 7.8 Film Processing, Editing, and Quality Grading in the Absence of the Senior Photographer

If Colleen Gillis is unavailable because of vacation, or an emergency that requires time away from her study responsibilities, the following back-up plan will facilitate the continuation of the study:

1. An assistant at Advanced Vision Institute, who will be trained personally by Ms. Gillis, will prepare the films for quality grading following the steps that are outlined in this manual in sections 7.3 and 7.4 (beginning with "Preparing the Rolls of Film for Processing by Colleen Gillis at Advanced Vision Institute").

2. The assistant will be prepared to recognize a camera malfunction (blank rolls of film) and notify the PI of a problem immediately. If the PI is unavailable for any reason, the assistant will notify Dr. Richard Kratz, M.D., the back up for the Senior Photographer.

3. If a camera malfunction is discovered after film processing, the PI or Richard Kratz, M.D will call the particular site to alert them of the problem, to determine the cause of the problem, and to ensure that it is corrected.

4. The assistant will ship the edited films and their corresponding Photography Log Forms via 2$^{ND}$ DAY to JSEI/UCLA where Richard Kratz, M.D. will quality grade the photographs and enter the data into the Access data base following the protocol outlined in this manual (beginning with "Quality Grading").
5. Ms. Gillis will be available during the duration of all photographic data collection by toll free pager number (877) 466-0073. However, if a photographer or site is unable to reach Ms. Gillis, Canon USA is also available for any photography questions or concerns. Our contact at Canon USA for technical support is Mr. Gary Rackler (972) 409-8872

## 7.9 Fundus Photograph Grading Protocol

INTRODUCTION

Fundus photographs will be used to assess the presence of age-related maculopathy. The grading system used for age-related maculopathy is a modification of the grading and classification system used in the Beaver Dam Eye Study and the Framingham Eye Study that was developed by the University of Wisconsin Reading Center for NHANES III.

MATERIALS USED IN GRADING

Graders will use:

a. Larson viewer and a 10X Peak Lupe with a mm measuring grid installed;
b. Logan #1055 light board, modified to hold two 14 watt "daylight" fluorescent tubes;
c. Field definition grid;
d. Two standard grids: Grid A for delineating 3 areas on the 45 degree fundus photos: area outside the arcade, the arcade area (8250 microns diameter- 5500 microns diameter in 30$^{o}$ photos) and central circle area (2250 microns diameter- 1500 microns diameter in 30$^{o}$ photos)*. Grid B for defining macula area for quality gradings (4500 microns diameter in 45 $^{o}$ photos– 3000 microns diameter in 30 $^{o}$ photos)*.

e. Standard circles for grading drusen area: $C_0$=95 microns diameter (63 microns diameter in 30° photos), $C_2$=375 microns diameter (250 microns diameter in 30° photos), $O_2$=960 microns diameter (640 microns diameter in 30° photos)*;
f. Two non-stereo 45-degree fundus photographs, mounted in plastic sheets, taken with a Canon non-mydriatic fundus camera;

(*The standard grid measurements are calculated based on measurements using grids developed for use in grading using a 30° degree camera)

Four 45° fundus photographs are available for each subject, two for each eye, along with two red reflex, external photographs, one for each eye. Since more than 1500 visit 6 images have been read, visit 8 fundus photographs will be graded using the same grading system developed for visit 6.

QUALITY GRADING

Fundus:

If a fundus photograph is present, the grade is 'Present', code "2"; if the fundus photograph is not present, the grade is 'Absent', code "0", STOP. When a photo is present, but the fundus is entirely obscured the fundus is graded as 'Absent', code "0". For instance, if there is no fundus detail visible and it is impossible to judge whether the fundus photograph is of a right or left eye, the photograph is considered absent. However, if any fundus detail is discernable and/or there is even a suggestion of a lesion, the grade is 'Present', code "2", and the proceeding items should be answered until another stop condition is met.

Focus:

Focus refers to the clarity of retinal image. Because of the importance of detecting lesions in the macular area, the grader is to consider focus in 75% or more of the macula area as defined by the 4500 microns diameter circle of grid B.

If retinal vessels are sharply defined or slightly fuzzy and small lesions, such as retinal microaneurysms and small drusen are visible, the grade is 'Good/Fair', or code "0". If clarity is decreased so that small retinal lesions might be missed but larger lesions, such as geographic atrophy, can be seen, the grade is 'Borderline', or code "1". If there is a pronounced decrease in sharpness, where detail of larger lesions cannot be recognized, the grade is 'Poor', or code "2".

Field Definition:

The photograph is positioned on the field definition grid. A fundus photograph with the optic disc positioned entirely within the dotted line of the grid is considered 'Good', code "0". The grader proceeds to whether artifacts are present. A fundus photograph with any portion of the optic disc positioned

between the dotted line and the solid line is considered 'Fair', code "1". A fundus photograph with any portion of the optic nerve positioned outside the solid line on the grid is considered 'Poor', code "2". A photograph with either 'Fair' or 'Poor' field definition is further defined in terms of Horizontal/Vertical Field Definition.

Field Definition Horizontal:

If the entire optic disc is within the dotted line of the grid, so that all of the optic disc, the macula and temporal retina are visible, the grade is 'Good', code "0". If any portion of the temporal edge of the optic disc is outside the dotted line of the grid, the grade is 'Temporal', code "1". If any portion of the nasal edge of the optic disc is outside the dotted line of the grid, the grade is 'Nasal', code "2". If horizontal field definition cannot be determined, the grade is 'CG', code "8".

Field Definition Vertical:

If the optic disc is entirely located within the dotted line of the grid, the grade is 'Good`, code "0". If any portion of the superior edge of the optic disc is outside the dotted line of the grid (that is, the vertical orientation is "high") the grade is `High', code "1". If any portion of the inferior edge of the optic disc is outside the dotted line of the grid, (that is, the vertical orientation is "low") the grade is 'Low', code "2". If the vertical field definition cannot be assessed, the grade is 'CG', code "8".

Artifacts Present:

If there is no artifact present, the grade is 'No', code "0". Proceed to whether the fundus is gradable or not (gradeability). If there is an artifact present, the grade is 'Yes', code "2", and the specific artifact(s) is/are checked in the appropriate item as:

Haze A green/white halo or partial halo, or a green/white cast throughout the photograph, see NHANES artifact examples;

Dust see NHANES artifact examples;

Lashes see NHANES artifact examples;

Arc A sharp edged band on the edge of the field ranging in color from white to orange, often blue tinged, usually extending no more than 180 degrees. See NHANES artifact examples;

Uneven Illumination, Center see NHANES artifact examples;

Uneven Illumination Edge see NHANES Standard #7B;

Central Dot Artifact see NHANES Standard #8;

Other if 'Other' is noted, describe the artifact in Comment section.

Gradeability:

If the whole field can be graded, the grade is code "0". If the disc cannot be graded, but it is possible to grade the macula, the grade is code "1", 'Disc ungradable'. If a portion of the macula $\geq O_2$ and less than 75% of macula (4500 diameter microns, Grid B) cannot be graded, but the disc is gradable, the grade is code "2", 'Portion macula ungradable'. If $\geq$ 75% of the macula area (4500 diameter microns, Grid B) is in 'Poor' focus, or is missing, or is obscured by a retinal hemorrhage, vitreous hemorrhage, asteroid hyalosis or some other condition and no lesion of any type is seen, but it is possible to grade the disc, the grade is code "3", 'Macula ungradable'. However, if any lesion is questionably present or present in the remaining 25% of the macula, the photo is graded and the appropriate gradeability is chosen (either code "2" or code "4"). If a portion of the disc and the macula are ungradable, the grade is code "4". If neither the disc nor the macula can be graded, but other portions of the eye are visible, the grade is code "5". If none of the field can be graded, the grade is code "6". If code "6" is chosen, STOP.

GENERAL PRINCIPLES WITH GRADING

All fundus images will be read by at least 2 graders. Discrepancies between graders in the level of ARM (level 10-60) will be adjudicated by Drs. Coleman or Fong. All graders will be masked to the findings at the other visit.

1 A lesion is definitely present if the grader is 90% or more sure.
2 A lesion is questionably present if the grader is 50% to 89% sure.
3 A lesion is absent if the grader is less than 50% sure.
4 Grids A and B are placed behind the slide.
5 Hard distinct/indistinct drusen are < standard circle $C_{0.}$
6 Soft distinct/indistinct drusen are ≥ standard circle $C_{0.}$

AGE-RELATED MACULAR DEGENERATION

Any Drusen Present

In order to assess further information about drusen, the grader must first answer the gatekeeper question code "2". If the eye can be graded and there are no drusen present within the field the grade is 'No', code "0". The grader then proceeds to the Comment Section.

If a drusen is present or questionably present anywhere in the field or there are some, but not all, items which should be listed as CG, code "8", the grade is 'Yes', code "2".

If it is impossible to assess whether a hard or soft drusen is present in 75% of the macula, using Grid B, 4500 µ diameter, and no drusen are present in the remaining 25% of the area, the grade is 'Can't Grade', code "8". In the situation where it is impossible to grade for hard drusen, but the grader is able to assess the presence or absence of soft drusen, a grade of 'Yes', code "2", is chosen. The grader should answer the hard drusen question "8" and consider the area questions as only referring to soft drusen.

Hard Drusen Present

Hard drusen are less than 95 µ in size by definition and thus the edges of hard drusen do not go outside the Standard circle $C_{0.}$ A drusen that is larger than $C_0$ is a soft drusen. If there are no hard, punctate retinal drusen present, the grade is code "0" and the grader goes on to Soft Drusen. If the grader is from 50% to 89% certain that there are hard drusen present (drusen that are subtle or are questionably present, Indistinct Hard Drusen) The grade is “Questionable”, code “1” in Visit 6. If there are definite hard drusen present anywhere in the field (90% or more certain), the grade is Distinct Hard Drusen - 'Yes', code "2". If $\geq$ 75% of the photograph cannot be graded, and no hard drusen are seen, the grade is 'CG', code "8".

Soft Drusen Present

If no soft drusen are present, that is, large drusen with distinct or indistinct margins (size is equal to or greater than Standard circle $C_0$), the grade is 'None', code "0". If the grader is from 50% to 89% certain there are soft drusen present anywhere in the photograph, the grader grades it as Questionable (code 1). If the grader sees soft drusen with hard edges anywhere in the photograph, the grade is Distinct Soft Drusen - 'Yes', code "2". If the grader sees soft drusen with indistinct, blurry edges anywhere in the photograph, the grade is Indistinct Soft Drusen – Yes, code “2”. If $\geq$ 75% of the photograph cannot be graded, and no soft drusen are seen, the grade is 'CG', code "8".

Central Circle-Soft Drusen Present

If there are no soft drusen present within the central circle area of the grid, the grade is 'None', code "0". If soft drusen are questionably present in this area of the grid, that is, the grader thinks the likelihood of presence of soft drusen is between 50-89%, the grade is code "1". If soft drusen are definitely present in the central circle area the grade is 'Yes', code "2". If 75% or more of the central circle area using Grid A cannot be graded, and the grader does not see soft drusen in the remaining 25%, the grade is 'CG', code "8".

Inner Circle-Soft Drusen Present

If there are no soft drusen present within the inner circle area of the grid, the grade is 'None', code "0". If soft drusen are questionably present in this area of the grid, that is, the grader thinks the likelihood of presence of soft drusen is between 50-89%, the grade is code "1". If soft drusen are definitely present in the inner circle area the grade is 'Yes', code "2". If 75% or more of the inner circle area using Grid A cannot be graded, and the grader does not see soft drusen in the remaining 25%, the grade is 'CG', code "8".

Central Circle Area

If no drusen are present within the central circle area of Grid A, mark 'None', code "0". If the total area of drusen within the central circle of the grid is: $<C_0$, the grade is code "1"; $<C_2$, the grade is code "2"; $<O_2$, the grade is code "3"; $\geq O_2$, the grade is code "4". If 75% or more of the central circle area of Grid A cannot be graded, and nothing is present in the remaining 25%, the grade is 'Can't Grade', code "8".

Inner Circle Area

If no drusen are present within the inner area, that is, between the central circle boundary and the outer edge of the grid, the grader chooses 'None', code "0". If the total area of drusen within the inner area of the grid is: $<C_0$, the grade is code "1"; $<C_2$, the grade is code "2"; $<O_2$, the grade is code "3"; $\geq O_2$, the grade is code "4". If 75% or more of the inner area of Grid A cannot be graded, and no drusen are present in the remaining 25%, the grade is 'CG', code "8".

Area Outside the Grid

The grader again looks at Grid A centered on the fovea. If there are no drusen present outside this grid, the grade is 'None', code "0". If definite 'hard and/or 'soft' drusen are present outside the grid, the grader again compares the total area outside the grid with the set of Standard Open Circles. 'Questionable' drusen are not included in estimates of area. If the total area of definite drusen outside the grid is < Std. $C_0$, the grade is code "1". If the total drusen area outside the grid is < Std. $C_2$, the grade is code "2". If the total drusen area outside the grid is < Std. $O_2$, the grade is code "3". If the total drusen area outside the grid is $\geq$ Std. $O_2$, the grade is code "4". If the drusen area outside the grid cannot be assessed, the grade is 'CG', code "8".

Increased Pigmentation

Deposition of granules or clumps of grey or black pigment in or beneath the retina. (NHANES Abnormalities Example #6).

RPE Depigmentation

Degeneration or depigmentation of retinal pigment epithelium characterized by faint grayish-yellow or pinkish-yellow areas of varying density and configuration without sharply defined borders. Increased or hyperpigmentation is frequently seen over and adjacent to these areas. (NHANES Abnormalities Example #1).

Geographic Atrophy

Sharply defined area of dropout of retinal pigment epithelium and choriocapillaries, exposing choroidal vessels. (NHANES Abnormalities Example #2).

Presence of Geographic Atrophy

Center circle: If the grader is 90% certain geographic atrophy is in the center circle then the grade is 'Present' or code "2."

Inner circle: If the grader is 90% certain geographic atrophy is in the inner circle then the grade is 'Present' or code "2."

Area $\geq C_2$? If the area of geographic atrophy is $\geq C_2$ then the grade is 'Yes' or code "2."

Fovea involved? If the geographic atrophy is under the area of the fovea then the grade is 'Yes' or code "2."

Sub-retinal Hemorrhage

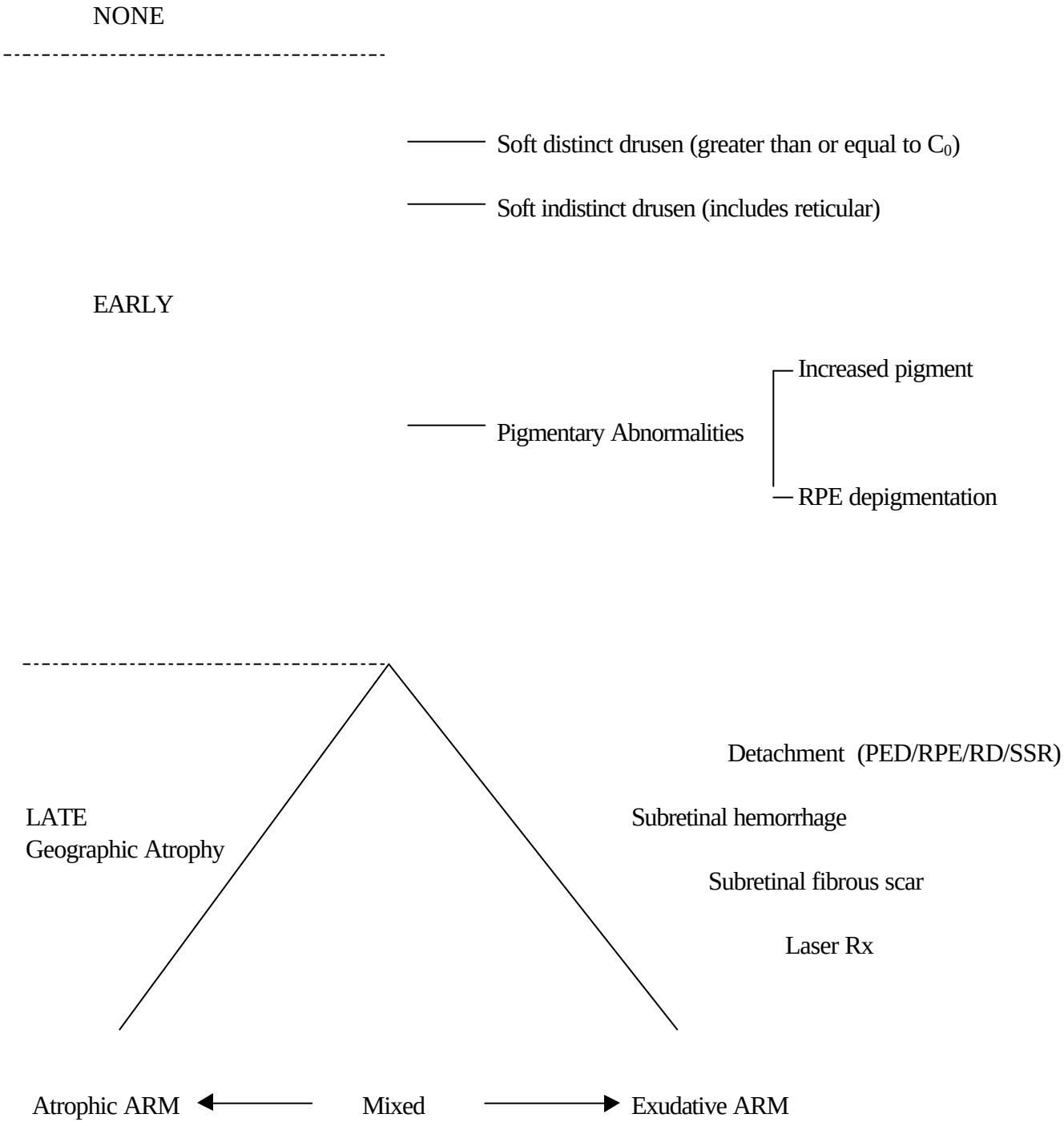
Hemorrhage below the retinal surface, which may appear as a dark red, dark grey or greenish area. (NHANES Abnormalities Example #3).

Sub-retinal Fibrous Scar

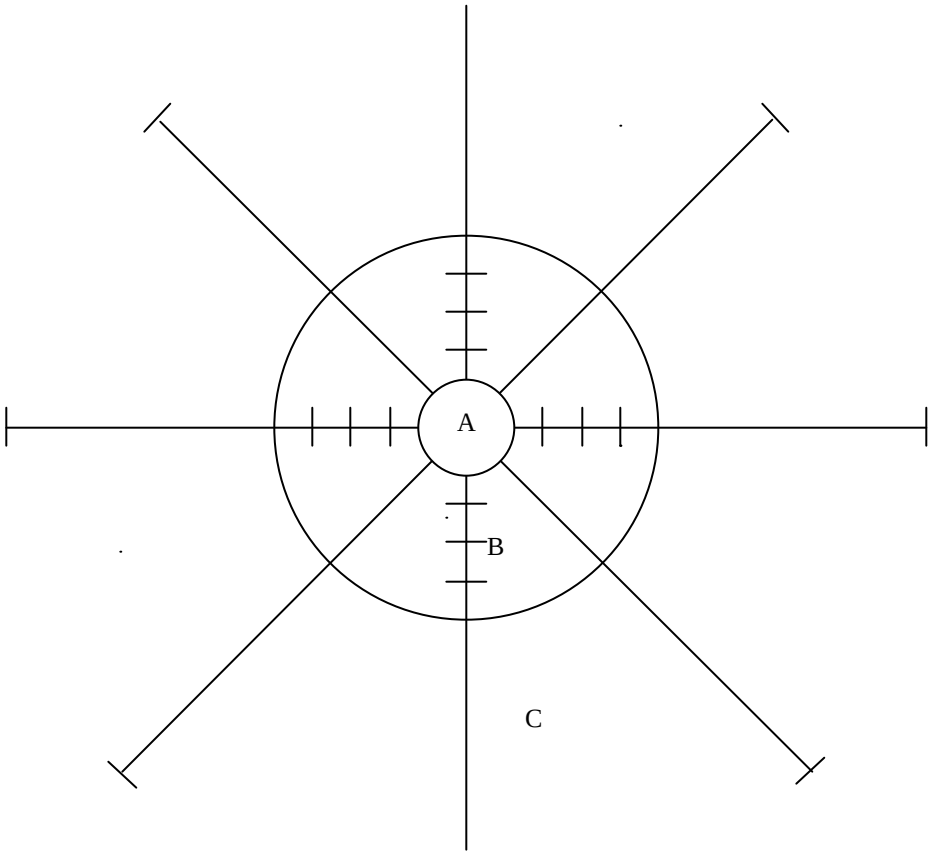
Sheets or mounds of "white" material appearing like a scar, involving the retina. (NHANES Abnormalities Example #4).

SSR Detachment

Clear or solid, dome shaped fluid filled elevation indicating a serous or retinal pigment epithelium detachment of the retina. (NHANES Abnormalities Example #5).


NONE
Soft distinct drusen (greater than or equal to $C_0$)
Soft indistinct drusen (includes reticular)
EARLY
Pigmentary Abnormalities
Increased pigment
RPE depigmentation
Detachment (PED/RPE/RD/SSR)
LATE
Geographic Atrophy
Subretinal hemorrhage
Subretinal fibrous scar
Laser Rx
Atrophic ARM
Mixed
Exudative ARM

## 7.10 Grid A:




A = Center Circle (2250 microns)
B = Inner Circle (microns)
C = Outside grid or Outside Arcade

# Incidence of Late Macular Degeneration in Older Women

# Photo Grading Form

Study ID: _____ Eye (R/L): _____ (1=Right, 2=Left)

Grader ID: _____ Date graded: _____/_____/_____

(1=CG, 2=RK, 3=ALC, 4=DF)

Photograph PRESENT (1/0): _____ If photograph PRESENT, enter "1". Otherwise, enter "0".

**FUNDUS**

**Optic Nerve**

Vertical Cup / Disc ratio: _____ (1: <0.4, 2: =0.4 and <0.7, 3: =0.7, 8: Can't evaluate)

Comment for optic disc: _____

**Macula Grading (Grid A only)**

Any drusen present? _____ (0=No, 1=Quest, 2=Yes, 8=CG)

Hard distinct drusen? _____

Soft distinct drusen? _____

Soft indistinct drusen? _____

Center circle soft drusen? _____

Inner circle soft drusen? _____

Outside grid area soft drusen? _____

Calcified drusen? _____

Reticular drusen? _____

Soft Distinct Drusen Area (0=None, 1= <$C_0$, 2= <$C_2$, 3= <$O_2$, 4= >$O_2$, 8=CG)

Center circle area _____ ($C_0$ = 63µ/95µ, $C_2$ = 250µ/375µ, $O_2$ = 640µ/960µ)

Inner circle area _____

Outside grid area _____

Soft Indistinct Drusen Area (0=None, 1= <$C_0$, 2= <$C_2$, 3= <$O_2$, 4= >$O_2$, 8=CG)

Center circle area _____ ($C_0$ = 63µ/95µ, $C_2$ = 250µ/375µ, $O_2$ = 640µ/960µ)

Inner circle area _____

Outside grid area _____

Drusen Area (Combined soft and hard drusen) (0=None, 1= <$C_0$, 2= <$C_2$, 3= <$O_2$, 4= >$O_2$, 8=CG)

Center circle area _____ ($C_0$ = 63µ/95µ, $C_2$ = 250µ/375µ, $O_2$ = 640µ/960µ)

Inner circle area _____

Outside grid area _____

Maculopathy (0=No, 1=Quest, 2=Yes, 8=CG)

Increased pigment _____

RPE depigmentation _____

Geographic atrophy:

Center circle: _____

Inner circle: _____

Area = $C_2$? _____

Fovea involved? _____

Sub-retinal hemorrhage _____

Sub-retinal fibrous scar _____

SSR detachment _____

PED detachment _____

| | FIELD (0=No, 1=Quest, 2=Yes) | CENTER CIRCLE (0=No, 2=Yes) |
|---|---|---|
| Rx for ARM | _____ | _____ |

Comments for Macula grading: _____

Diabetic Retinopathy? _____ 0=None, 1=Quest, 2=Yes, 8=CG

Vascular abnormal? _____ 0=None, 1=Quest, 2=Yes, 8=CG

| **Other Abnormalities?** | FIELD (0=No, 1=Quest, 2=Yes) | CENTER CIRCLE (0=No, 2=Yes) |
|---|---|---|
| Angioid Streaks | _____ | _____ |
| Chorioret Abnorm/other | _____ | _____ |
| Br/Cent Artery Occlus | _____ | _____ |
| Br/Cent Vein Occlus | _____ | _____ |
| Arteriolar changes | _____ | _____ |
| Significant A/V Nicking | _____ | _____ |
| Hollenhorst Plaque | _____ | _____ |
| Asteroid Hyalosis | _____ | _____ |

| | | |
|---|---|---|
| Nevus | _____ | _____ |
| Surface Wrinkling Ret | _____ | _____ |
| Histoplasmosis (POHS) | _____ | _____ |
| Retinal detachment | _____ | _____ |
| Laser Rx /Other | _____ | _____ |
| Pseudovitelleform | _____ | _____ |
| Macular hole/pseudohole | _____ | _____ |
| Myopic degeneration | _____ | _____ |
| Glial/cellophane | _____ | _____ |
| Retinal dystrophies | _____ | _____ |

Other (list in comments): _____

**LENS.**

Aphakic / Pseudophakic PRESENT (1/0):_____ If Aphakic / Pseudophakic PRESENT, enter "1". Otherwise, enter "0".

Marcher (0=No, 1=Quest, 2=Yes, 8=CG)

- No opacities present _____
- Small peripheral, no central _____
- Moderate peripheral or some central (cortical or PSC) _____
- Extensive central opacity (cortical or PSC) _____
- IOL, no secondary opacity _____
- IOL with secondary opacity _____

Topcon: (0=No, 1=Quest, 2=Yes, 8=CG)

- Less than Std 4 _____
- Greater than Std 4 _____

**Summary of Data Management System**

The SOF data system consists of three related components: DATA INPUT, DATA QUERYING, and QUERY ADDRESSING. The Clinical Sites are the main part in completing DATA INPUT. The study staff from the 4 clinical sites (Baltimore, Minneapolis, Pittsburgh and Portland) are responsible for taking fundus photos from patients; collect questionnaire, clinic exam, and vision exam data on machine-readable forms. Then the forms are digitally sent via internet (fax/ scan) into the UCSF Coordinating Center database. Reports on the study web site provide feedback on the data input process. The second component is DATA QUERYING (or the edit report). It consists primarily of a query generation program that is run several times a day against the entire database. The results are available on the study web site. The web site also provides a means whereby study staff or sponsor can originate their own queries (i.e. potential errors or missing data). The third component is QUERY ADDRESSING. Using the "edit report" (query list) on the web site as the gatekeeper, study staff is able to make changes to the data both on paper forms at site and in the study database in order to fix errors or inconsistencies in the data via internet. All changes are initialed and dated.

Among the SOF data, vision related SAS data sets are transferred to UCLA coordinating center from UCSF monthly. UCLA will be responsible for vision related data cleaning and quality control. That is including: rerun range checks on possible values of relevant variables; check data consistency among relevant variables; examine data quality and contact the site if their values are not in accordance with the other sites. The same DATA QUERY and QUERY ADDRESSING procedures are followed by UCLA via the study web site.

The fundus photos are sent to Ms. Gillis directly from the clinical sites. Two steps are taken in order to set up the final photo grades data set: PHOTO SCREENING & GRADING, DATA SET COMBINING & ADJUDICATION. The senior photographer screens the photos for quality. Queries that are generated by the senior photographer are communicated with the Principle Investigator (PI) and the photographers at site. The fundus photographs are sent to UCLA Coordinating Center. Two trained graders then grade the photographs independently. The 2 data sets generated by the 2 graders independently are then combined together and adjudicated by the PI monthly for any discrepancies. A final photo set is created. External validity with the University of Wisconsin Reading Center is conducted every 6 months after year 2 for 30% of cases and 10% of noncases in the final data set.

## Vision related data cleaning and quality control at UCLA

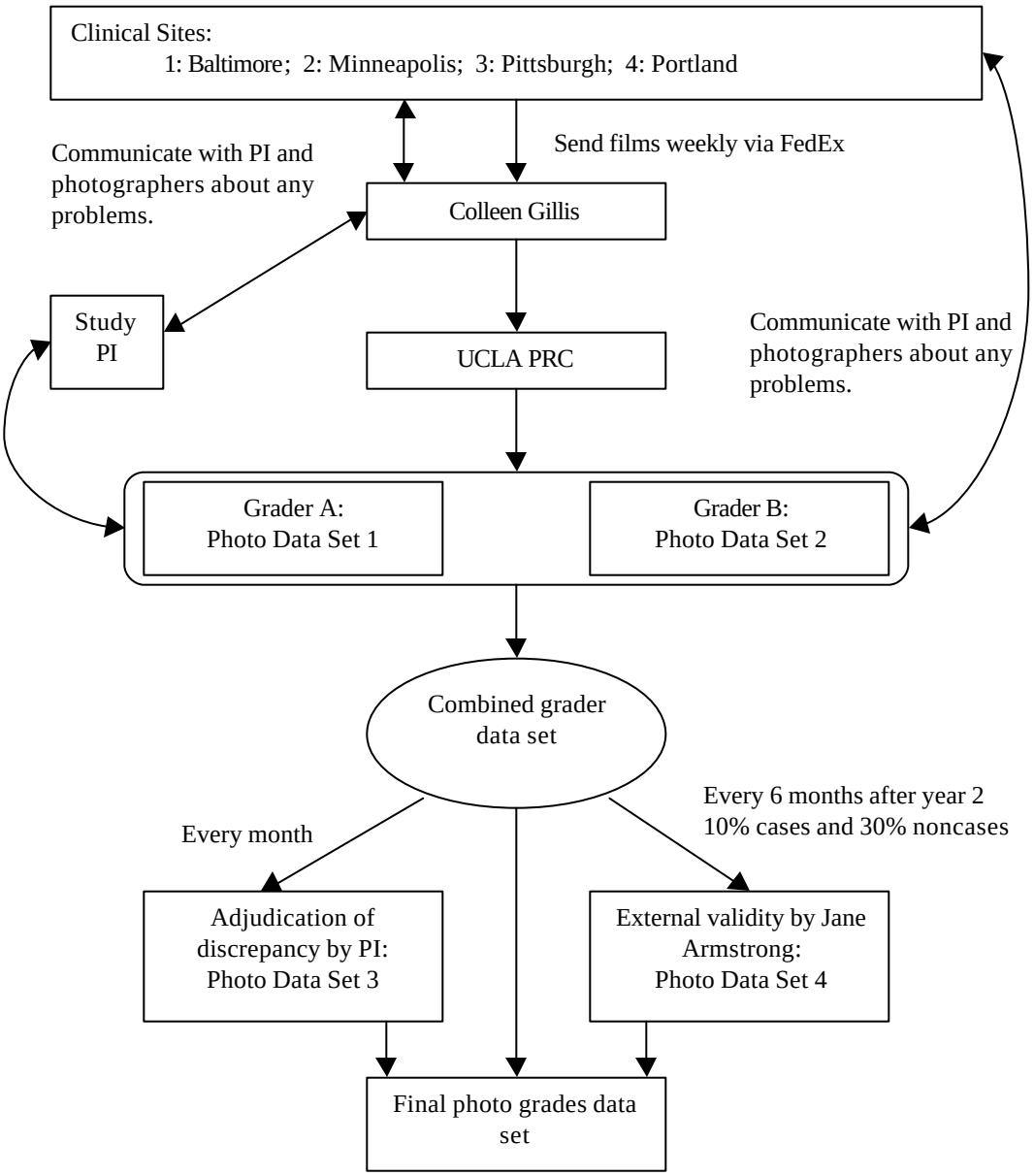
| Tasks | Item | Contents |
|---|---|---|
| **Range checks** | Ocular History | Number of eye related surgeries |
| | Contrast Sensitivity | Number of circles correctly identified |
| | Humphrey Autorefractor | 1. Visual acuity<br>2. Autorefractor |
| | Intraocular Pressure | Avg. IOP |
| | Eye Photo | 1. Film roll #:<br>2. Film type |
| **Data consistency** | Blind eye | Same blind record in Ocular History, Contrast Sensitivity test and -Functional Vision test |
| | Enucleation | 1. Same blind record in Ocular History, Contrast Sensitivity test and Functional Vision test<br>2. Result not available for Humphrey Autorefractor, Intraocular Pressure and Eye Photo |
| | Contrast Sensitivity & Functional Vision | 1. No result if a test not done<br>2. If unable to read chart at 5 feet in one test, the other should be same.<br>3. Both test should use the same distance<br>4. Both test should use the same corrective aids |
| | Eye surgery history | Consistent record should be on Ocular History and Intraocular Pressure page |
| **Data quality** | Missing rate | Humphrey autorefractor, visual acuity and contrast sensitivity |
| | Dilation amount across sites | |
| | Completion rates of vision measures across sites. | |

| | |
|---|---|
| Fundus photographs | 1. Quality graded if photo taken<br>2. Quality grades |

Mean values of visual acuity and contrast sensitivity across sites

# SOF-AMD Photography Reading Center (PRC)

## Flow Chart for Data Management



## Statistical Issues

General analytic approach.

## Unit of Analysis

The unit of data analysis will be either study subjects or eyes, depending on the goal of each analysis. When an outcome is an eye-specified event, such as the late ARM or the ARM progression, we will systematically analyze one eye from each subject separately, such as right eye or left eye, or best eye or worst eye. When both eyes are included in the analysis, we will use statistical methods that could take into account the potential positive correlation between eyes, such as the GEE approach. When an outcome is a subject-specified event, such as the quality of life (NEI-VFQ) the fractures, and a potential risk factor is an eye-related measurement, such as cataract surgery, we will classify the risk factor as none, a one-eye event, or a two-eye event whenever possible.

## Analytic Plan

First, we will obtain descriptive statistics on all relevant outcomes and risk factors. The descriptive statistics for continuously scaled variables include means, standard deviations, medians, quartiles, and ranges; the descriptive statistics for categorical variables are their frequencies and percentages. We will examine crude (unadjusted) associations between each outcome and a potential risk factor. Depending on the type of variables, the crude associations will be based on correlation coefficients, T-tests/ANOVA tests, Chi-square tests, and univariate regression models. Finally, since our study is not a randomized study, it is important for us to control for multiple risk factors and potential confounding factors. Thus, we will estimate adjusted measures of effects using multiple regression models, stratified analyses (e.g., age group, parity, visual acuity), and/or other advanced statistical methods, such as multiple imputations or Bayesian analyses. A potential confounder will be determined based on investigators' prior knowledge and empirical associations between outcomes and primary risk factors ($P < 0.25$). In addition, we will develop advanced statistical methods for data analyses, if we find that the existing statistical methods do not fully address our problems.

## Outcome assessment

Primary Endpoints

Our primary endpoints are 5-year incidence of late ARM and 5-year progression rate of ARM after Visit 6. A 6-level severity scale of ARM is defined as following:

- Level 10 = no drusen, or hard drusen or small drusen <95 microns in diameter only, regardless of area of involvement, and no pigmentary abnormality present
- Level 20 = hard drusen or small drusen <95 microns in diameter, regardless of area of involvement, with increased retinal pigment present but no RPE depigmentation or soft drusen (≥ 95 microns) with drusen area less than 960 microns and no pigment abnormalities present
- Level 30 = soft drusen (≥95 microns) with drusen area less than 960 microns and RPE depigmentation present or soft drusen with drusen area greater than or equal to 960 microns with or without increased retinal pigment but no RPE depigmentation
- Level 40 = soft drusen (≥ 95 microns) with drusen area greater than or equal to 960 microns and RPE depigmentation present with or without increased retinal pigment
- Level 50 = geographic atrophy under the fovea
- Level 60 = exudative macular degeneration with or without geographic atrophy present

The incidence of late ARM is the development of any of the following after Visit 6 among subjects who did not have levels 50 or 60 at Visit 6:

- Exudative macular degeneration
- Geographic atrophy

The progression of ARM is the development of any of the following after Visit 6 among subjects whose ARM level was level 10 through level 50 at Visit 6:

- Increase in severity by 2 steps or more from level 10 through 30
- Increase in severity by 1 step or more from level 40 or 50

Additional Endpoints

Additional endpoints include 5-year progression rate from early to late ARM and 5-year incidence of early ARM after Visit 6. The progression from early to late ARM is the development of any of the following after Visit 6 among subjects whose ARM level was level 20 through 40 at Visit 6:

- Increase in severity from levels 20-40 to levels 50-60

The incidence of early ARM is the development of any of the following after Visit 6 among subjects whose ARM level was below level 30 at Visit 6:

- Presence of soft indistinct drusen
- Presence of any type of drusen associated with RPE depigmentation
- Increased RPE pigment

**Background Related to Endpoints**

Based on our preliminary findings from the SOF Visit 6, among 1808 subjects whose fundus photographs were graded at Visit 6, 54 (3.0%) were not able to be graded in both eyes, 130 (7.2%) had level 0 in both eyes, 141 (7.8%) had level 10 in at least one eye, 1464 (81.0%) had levels 20 to 40 in at least one eye, 19 (1.1%) had levels 50 or 60 in at least one eye.

Information on the incidence of late ARM and progression of ARM are available from previous studies. In the Beaver Dam Eye Study, there were 24 eyes with late ARM among 189 eyes from study participants who were 75 years or older. Their estimate of incidence of late ARM is 12.7%. In the Blue Mountains Eye Study, there were 6 eyes with late ARM in 68 eyes from women who were 80 years or older (an estimated 8.8% incidence of late ARM). Assuming a 12.7% incidence of late ARM, we anticipate 378 cases of late ARM in our cohort (=3094*0.960*0.127).

In the Beaver Dam Eye Study, there were 66 eyes who developed ARM progression among 584 eyes from study participants who were 75 years or older (an estimated progression rate of 11.3%). Based on this estimate, we anticipate 310 cases of ARM progression in our cohort (=3094*0.887*0.113).

**Primary Specific Aim 1**

**To estimate the 5-year incidence of late ARM and the 5-year progression rate of ARM after Visit 6 and to explore the pathogenesis of late ARM by analyzing potential risk factors for new or progressive ARM.**

We will estimate the incidence/progression rates separately for right eye, left eye, best eye, worst eye, and both eyes combined. Since ARM severity will be determined by the quality of fundus photographs, the rate of ungradeable photographs will be very important. If the ungradeable rate is low (less than 5%), we will assume that those ungradeable photos are missing at random and exclude them from our analyses. However, if the ungradeable rate is high (more than 10%), we will perform both complete data analysis (excluding those ungradeable photos) and multiple imputation analyses (imputing the ARM status based on all relevant information). Confidence intervals (CI) for the incidence/progression rate will be obtained from the estimates of logistic regression models. Since the estimates/CIs obtained from logistic regression models are estimates for odds of being a case instead of rates, we will approximate the rate estimates/CIs with the estimates directly if the rate estimate is low (less than 10%). If the rate is high (more than 15%), the estimates/CIs for odds will be converted to the rate estimates/CIs using the conversion formula: RATE = exp(ODDS)/(1+exp(ODDS)).

First, we will estimate the 5-year incidence of late ARM and the 5-year progression rate of ARM by dividing the total number of new/progressed ARM cases found in Visit 8 by the total number of available eyes from study participants.

Second, we will estimate the stratified and adjusted 5-year incidence/progression rates. Potential stratification/adjusted variables include age, smoking status, alcohol consumption, BMI, prior cataract surgery, systemic diseases (e.g. heart disease and diabetes) and ocular diseases (e.g. cataract and glaucoma). We will use the information obtained at Visit 6 for those variables because of the time ambiguity of the information obtained at Visit 8 when the endpoint is reached.

Finally, we will conduct risk factor analyses for 5-year incidence/progression rates. We will proceed as described earlier in the section of general analytic approach. Univariate and multivariate logistic regression models will be used in this step. Primary risk factors include:

- Smoking: Smoking status will be obtained from questionnaires, and will be classified as non-smokers or current smokers. Potential confounders for smoking status are age, alcohol consumption, and BMI.
- Alcohol use: Alcohol consumption will be obtained from questionnaires, amd will be summarized by number of drinks per week. Potential confounders for alcohol use are age, smoking status, BMI, and blood pressure.
- Diet: (Antioxidants, Fat intakes, and Cholesterol): Information on diet intake will be measured from dietary history questionnaires obtained at visit 6. Potential confounders for diets are age, smoking status, alcohol consumption, BMI, and blood pressure.
- Prior cataract surgery: Prior cataract surgery will be assessed in 2 ways: Self-report of prior cataract surgery including time of surgery and anterior segment photographs. Self-report of prior cataract surgery will based on the post cards mailed to each subject every 12 weeks, so we will have reliable responses with minimal recall bias. Information obtained from self-report will be verified with anterior segment photographs. We will perform both “Beaver-Dam-style” analysis and enhanced “Beaver-Dam-style” analysis. In “Beaver-Dam-style” analysis, we will proceed as described in the general analytic approach, and we will conduct stratified analyses within each stratum defined by each potential confounder. In enhanced “Beaver-Dam-style” analysis, we will include time since cataract surgery as an additional potential confounder, and we will stratify by ARM status measured at Visit-6 and control for time since cataract surgery. Potential confounders for diabetes are age, smoking status, alcohol consumption, BMI, and blood pressure. To address potential selection bias, we will supplement with propensity score analysis on propensity for cataract surgery. In propensity score analysis, subjects will first be divided into subgroups according to their probabilities of having a cataract surgery, which will be estimated from available demographic and relevant clinic information. The incidence/progression rates will then be compared within each subgroup, and weighted estimates will be obtained by combining all subgroups.
- Diabetes: Diabetes has been assessed in 2 ways: Self-report and fructosamine levels. Potential confounders for diabetes are age, smoking status, alcohol consumption, BMI, and

blood pressure. Analysis will be only performed on existing fructosamine samples as a pilot study.

- Endogenous Estrogen: Endogenous estrogen has been measured from serum samples using liquid-liquid organic extraction, column chromatography, and radioimmunoassay. Potential confounders for endogenous estrogen are age, smoking status, alcohol consumption, BMI, and blood pressure. Analysis will be only performed on existing estrogen samples as a pilot study.

**Primary Specific Aim 2**

**To describe the change in visual function (acuity and contrast sensitivity) over 14 years in older women and to examine potential risk factors for loss of visual function.**

The visual function is measured by both acuity using Bailey-Lovie chart and contrast sensitivity. We will analyze both continuous outcome variables and binary outcome variables for changes in visual function. A binary variable for loss of visual acuity will be defined as loss of 10 or more letters between baseline and Visit 8, and the continuous outcome variable for visual acuity will be the number of letters read in the Bailey-Lovie chart. However, because continuous measures of change in visual acuity may be more sensitive than a binary indicator of change, we will also perform sensitivity analyses with the log transformed minimum angle of resolution (logMAR) scores of Bailey-Lovie (calculated as 1.7 – 0.02 [BL+30]) to see if the loss of visual function are confirmed. To be consistent with published data, we will use log contrast sensitivity values for low and high spatial frequency contrast sensitivity.

We will estimate overall changes in visual function, and report the changes separately for right eye, left eye, best eye, worst eye, and both eyes combined. We will proceed as described earlier in the section of general analytic approach. Univariate and multivariate linear regression models will be applied for continuous outcome variables, and univariate and multivariate logistic regression models will be applied for binary outcome variable. Repeated-measurement models will also be used to explore the patterns of visual function changes from baseline to Visit 8.

In SOF, at Visit 1 (Year 1 or Baseline Examination), 93% of subjects had visual acuity better than 20/40, 7% had visual acuity of 20/40 to better than 20/80, and 0.1% had visual acuity of 20/80 or worse. At Visit 6, 71% of subjects had visual acuity of better than 20/40, 24% had visual acuity of 20/40 to better than 20/80, and 5% had visual acuity of 20/80 or worse. Assuming 3094 subjects have visual acuity measures at Visits 6 and 8 and that the standard deviation of an increase in percentage decline of visual acuity from Visit 6 to 8 is 0.433 (=sqrt(0.25*(1-0.25)), the minimum detectable increase in percentage vision decline from Visit 6 to 8 is 2.2% for 80% power and 2.5% for 90% power.

**Secondary Specific Aims**

**To test the hypotheses that progression of ARM is associated with an increase risk of non-spine fractures and to describe the influence of severity and progression of ARM on vision-targeted health-related quality of life**

To study the association between the incidence of late ARM and the progression of ARM and the risk of falls and fractures in elderly women, our outcome variable will be time to non-spine fracture. We will proceed as described earlier in the section of general analytic approach. For fracture endpoints, we will perform Cox proportional hazards regression models to examine the hypotheses that progression in ARM (from Visit 6 to Visit 8) is associated with increased risks of non-spine fractures occurring subsequent to Visit 8 (Year 14 Examination), after adjusting for age and other potential fracture risk factors previously identified and published from SOF.

As we discussed earlier, we will expect 3,094 subjects to have gradeable photographs at Visit 8 (Year 14 Examination), and 340 cases of ARM progression and 375 new cases of late ARM. If we there are 345 non-spine fractures (0.115/5 years) after Visit 8 (Year 14 Examination) among participants at risk of ARM progression, the relative risk that we will be able to detect with a one-sided test and alpha of 0.025 (two-sided alpha of 0.05) is 1.57 for 80% power and 1.68 for 90% power. The relative risk for non-spine fracture among patients with incident late ARM would be 1.54 for 80% power and 1.64 for 90% power, assuming 345 non-spine fractures (0.115/5 years) among the early ARM patients.

To describe the influence of severity and progression of ARM on vision-targeted health-related quality of life and change in vision-targeted health-related quality of life, our outcome variable for vision-targeted health related quality of life is measured with 9 –item NEI-VFQ developed for NHANES IV. We will proceed as described earlier in the section of general analytic approach using bivariate analyses and linear regression models

Because demographic characteristics, such as age, may independently affect the NEI-VFQ scores, we will also construct multivariate linear regression models to adjust for the independent effects of other patient-level characteristics while examining the main effect of ARM severity.