D R A F T

Framingham Eye Study II

(FES II)

MANUAL OF PROCEDURES

January 1988

7/29/87

FRAMINGHAM EYE STUDY II

Manual of Procedures

• : In development

CHAPTER 1. Introduction

1.1 OVERVIEW

In 1973-75, 2675 members of the Framingham Heart Study (FHS) cohort were examined for senile cataract, senile macular degeneration, diabetic retinopathy, and glaucoma. Prevalence of these four conditions was estimated, and associations between prevalence and potential risk factors have been investigated, using ocular variables as well as variables measured previously and concurrently in the Heart Study.

The approximately 1500 surviving members of the cohort who received the 1973-75 Framingham Eye Study (FES) eye examination will be re-examined for age-related lens and macular changes, providing data that, in conjunction with the earlier data, can be used to:

a) Calculate incidence rates for both age-related macular degeneration and senile cataract.
b) Describe the natural history, or progression, of these two conditions.
c) Identify associations between the presence and the progression of these conditions and Heart Study variables whose values were determined before development or progression of these diseases.

The examination consists of clinical evaluation of the lens and the macular area of the retina, through dilated pupils, by direct and indirect

ophthalmoscopy and by slit lamp biomicroscopy; and retinal photography of the disc and macular regions. Visual acuity is measured by automated refractometry. Photographs are sent to a reading center for grading.

Epistat Associates, Inc., Hanover, NH, was awarded a contract in January, 1986, to perform ocular re-examination of the FES subjects. Examinations began in August, 1986.

The Fundus Photograph Reading Center, University of Wisconsin, Madison, WI, received a contract in June, 1986, to develop and apply a photograph grading system for age-related macular degeneration to the fundus photographs from the 1973 study and the present study. The grading system was completed and approved in February, 1987.

Data management is done by NEI's contractor, Group Operations, Inc., Washington, DC, through its Rockville, MD, office.

Examinations are done at the FHS site, Framingham, MA, in close coordination with the Framingham Heart Study, the NHLBI, and their FHS contractor (Boston University).

The study is projected to continue through 1988.

1.2 ORGANIZATION

1.2.1 PRINCIPAL PARTICIPANTS

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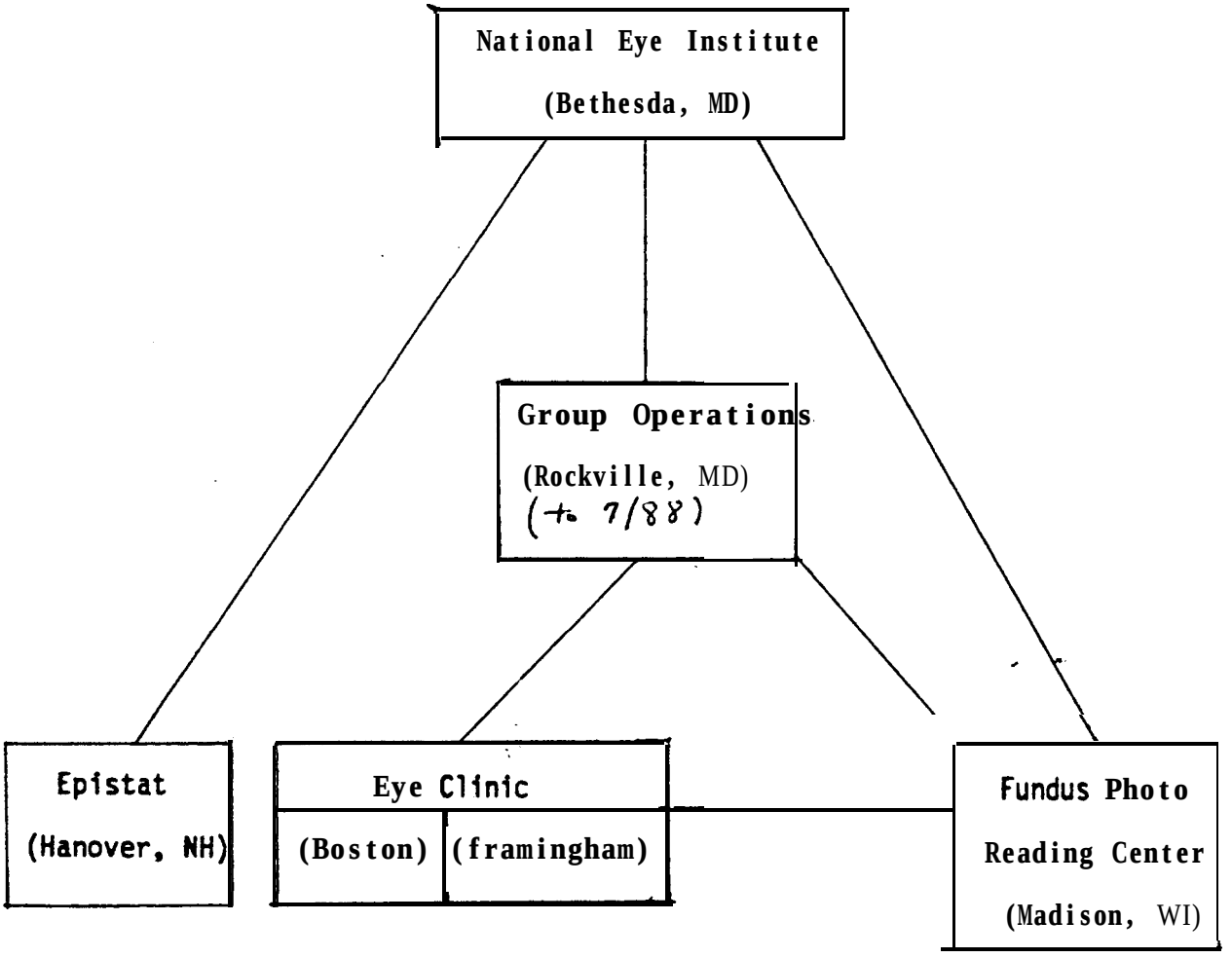
1.2.2 ORGANIZATION



CHAPTER 3

PROCEDURES FOR OCULAR EXAMINATIONS

3.1 INTRODUCTION

The purpose of the ocular examination of FES subjects is to evaluate the ocular characteristics of examinees relative to two disorders: senile cataract and age-related macular disease. During the examination, the examiner will assess each eye for the presence, type, severity, etc. of those disorders. For senile cataract the examiner's assessment will stand alone, but for age-related macular disease that assessment will be substantiated for comparison (in the analysis stage of the study) with the grading of macular photographs for the presence of lesions associated with age-related macular degeneration.

This protocol for the ocular examination is designed to describe the methods used to assess the presence of the two ocular diseases. First, the data should accurately reflect the disease status of each eye in a way that has clinical relevance. Second, and equally important, the data should provide measurements that are comparable to those taken during the first FES examination.

In a large epidemiology study such as this, there is a great opportunity for potential errors to become manifest. This is particularly true when more than one examiner participates In the study. A patient examination performed as part of an epidemiology study must be conducted In a different fashion and different frame of mind than a clinical office examination.

A study patient must be examined according to a set procedure that cannot vary from patient to patient or with time. The technique of examination and criteria for filling out the examination form must be Identical for all

examiners participating in the study. The protocol must be strictly adhered to and extreme care must be taken In examining the patient and filling out the form. It is recommended that the protocol be reviewed periodically to keep the points fresh in your memory. The protocol is necessarily long in order to maintain consistency and reduce the examiner variability.

When filling out the form, please use ink, and specifically do not use either pencil or red ink. Pencil marks tend to blur with use. 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 describing the correct entry.

In general, each examination will be done by two examiners. The first examiner will do Part I and the second examiner will record the data for Part I. The second examiner will then do Part II and 'the first examiner will record the data for Part II. The first examiner will then do the photography while the second examiner rechecks the form to be certain that it has been filled out completely and accurately.

3.2 PART I

3.2.1 PATIENT IDENTIFICATION: The examinee's Framingham Record Number, date of birth, date of examination, place of examination, and the name (and address, if not local) of examinee's private ophthalmologist or other eye care provider or family physician to whom a report will be sent, will be filled in when the patient is first registered for the eye examination. Under the place of examination, 1 = "clinic" refers to the Framingham Eye Study examining rooms across from the Framingham Union Hospital; 2 = "local" refers to any

exam done by the FES staff outside the "clinic", e.g., in the examinee's home, nursing home, hospital, etc.; 3 = "elsewhere" refers to an exam done on individuals who are unable to return to the Framingham areas for examination.

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 "Have you ever had an eye removed?" If the patient indicates that s/he has had an eye removed, determine which eye and record *on* the form. This question includes enucleation and phthisis bulbi (a blind eye which is obviously smaller than normal).

3.2.2 VISUAL ACUITY: Visual acuity measurement is done first with the patient's present refractive correction or so-called "walk-in" visual acuity. Both an objective and a subjective refraction and the accompanying visual acuities are then obtained. This information will be communicated in writing to the examinee's eye care specialist, if one is available.

The refraction and the visual acuity measurements are performed using the Humphrey Autorefractor. This is best done with all extraneous light turned off in the room, using the lighted visual acuity chart of the autorefractor.

3.2.2.1 "Walk-In" Visual Acuity: Visual acuity is measured with the Humphrey Autorefractor. If distance glasses or contact lenses are normally used and are available at the time of examination, these should be worn. Do not test near vision. Begin with the 20/40 line if the acuity seems to be good and present increasingly smaller lines until half a line cannot be read correctly. When *two* letters or more are missed on a line, ask the subject to read the complete line again, more slowly. If the missed letter or letters are correctly identified on the second reading, that line will be accepted as correctly read. When the subject volunteers two or three alternative designations of the letter, ask the subject to commit him/herself to a

definite answer. If, on the second reading, a different letter is now read wrong, do not give credit for this letter or any others that are guessed wrongly on the second reading. The vision will be recorded as the smallest line read correctly by each with one error or less. Any additional letters correctly identified on lower lines will be recorded with a plus, e.g. 20/25+3.

In cases where the distance vision is < 20/400, record vision as "finger counting", "hand motion", "light perception", or "no light perception." Finger counting is tested by holding two or three fingers two feet from the patient and should be recorded as 9/400. Hand motion is tested by moving a hand back and forth in front of the patient with the other eye occluded. This is recorded as 8/400. Light perception should be tested by carefully occluding the fellow eye and directing the light of the indirect ophthalmoscope at full intensity at the examinee's eye from about a one-foot distance. This is recorded as 7/400. No light perception is recorded as 2/400.

Once "walk-in" visual acuity is completed, distance correction (spectacles or contact lenses),.is then removed for an objective refraction with the Humphrey Autorefractor. Record the results of the objective refraction if 20/20 can be obtained. If 20/20 is not achieved, a subjective refraction is performed, based on the objective refraction. Additional ±0.50 sphere are gfven to determine if the patient sees improvement. This process is continued until the patient says it makes the vision worse. The power and the axis of the cylinder is changed to determine If there is further improvement or worsening.

Very rarely, ocular conditions such as aphakia may require trial lens refraction. If, due to physical or mental limitations of the examinee, it Is

not possible to use the Humphrey Autorefractor, then a trial lens refraction will also be done using a projected visual acuity chart.

The best corrected visual acuity should be recorded as the best visual acuity obtained using the walk-in correction, the objective refraction, or the subjective refraction.

3.2.3 ANGLE DEPTHS: The depth of the anterior chamber is assessed to determine if there is any danger in dilating the pupil.

The slit beam of the Haag Streit slit-lamp is placed almost perpendicular to the peripheral cornea1 surface and the angle opening is viewed at a 60 degree angle from the light beam. The light beam should be as narrow as possible, and the area of measurement is located just before the point of disappearance of the corneal-iris space at the periphery. The angle should be viewed with the slit-lamp magnification set at 10D. The temporal anterior chamber angle at either the 3 o'clock (OS) or 9 o'clock (OD) meridian should be the approximate area evaluated. If the angle is estimated as 10 degrees or less in any quadrant, do not dilate but attempt to continue the examination through an undilated pupil. However, if the patient has been dilated within the past two years with no problems, dilation may proceed after consulting the patient's ophthalmologist.

In addition, as a double check, angle depth should be estimated with a pen light. The pen light is held several Inches from the temporal llmbus of the cornea with its light beam traversing horizontally across the anterior chamber of the eye. In patients with wide open angles, the light will be seen from the temporal limbus to the nasal llmbus. If the chamber is shallow, a shadow will be cast onto the nasal Iris due to the bowing forward of the

lense-iris diaphram 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. Am J Ophthalmol 68:625-629, 1969.1

3.2.4. INTRAOCULAR PRESSURE: Intraocular pressure is measured in both eyes using an applanation tonometer before the pupils are dilated. Instill 1 drop of combined proparacaine and fluorescein into the lower fornix bilaterally. Avoid contact with lashes or lid margins. Slit-lamp is set at 10x magnification. The illumination aperture should be fully positioned 60" to the slit-lamp. Turn measuring scale of the Goldman tonometer to 10 mm Hg.

Bring the prism in contact with the cornea - the point at which the limbus shines with a bluish light, observed with the naked eye from the side opposite to the illumination. Correct the position so that the two semicircles are of equal size and located in the 'middle of the field of view.

It is important that the mires be of medium width. If the examiner has the impression of thick mires, the following procedure should be followed in sequence until the mires are of required width.

a - Check that the upper 'lid is not resting on tonometer.

b - Pull back the tonometer and reposition.

C - Blink eyes.

d - Wipe tonometer head.

e - Blot lacrimal lake of the lower fornix.

When the mires are too thin after administering the first drop of combined proparacaine and fluorescein, adminlster a second drop.

To determine the Intraocular pressure turn the measuring drum on the tonometer until the inner borders of the two fluorescein rings just touch each

other at the midpoint of the ocular pulse. The mires should both overlap and separate with the pulse swing. When the swing is equidistant on either side of the midpoint record the pressure from the measuring drum to the nearest millimeter of mercury. The measuring dial should not be observed until the endpoint is reached in order to keep the measurement objective.

3.2.5 IRIS COLOR: Iris color should be determined using the following procedure:

A. Prior to the classification scheme, the level of illumination should be checked. The same type of illumination should be used to evaluate each patient in the study.

B. Iris pigmentation is classified in a two step process.

1. Classify the patient's predominant pigmentation as either a. blue/green (light pigmentation) by b. brown/black (dark pigmentation).

2. If the patient's predominant pigmentation is blue/green and: a. additional pigmentation is yellow, dark or navy blue, dark green, or dark grey, classification remains blue/green; b. additional pigmentation is brown or black, classification is changed to mixed (medium pigmentation).

3. If the patient's predominant pigmentation is brown/black; and: a. additional pigmentation is brown or black, classification remains brown/black: b. additional pigmentation is yellow, green, red or orange, classification is changed to nixed.

4. Record final classification as either blue (light pigmentation), mixed (medium pigmentation), or brown (dark pigmentation).

3.2.6. PUPIL DILATION: First, record the time of day of dilation. Then dilate both eyes with one drop of 1% tropicamide and 2.5% phenylephrine. This may be repeated once after ten minutes. While the eyes are dilating, the Patient may go back to the central waitlng area or continue to the next

station in the Heart Study exam. After a period of 20 to 30 minutes, when the eyes are fully dilated, the examinee will be brought back by examiner 1 for the remainder of the examination.

3.3 PART II

Dilation will be considered adequate when approximately two-thirds of the diameter of the anterior surface of the lens can be visualized while examining the eye with the Haag Streight Slit-Lamp. If pupil constriction occurs to the point that this portion of the lens cannot be visualized, give the examinee an additional drop and wait another 5-10 minutes before continuing the examination. Record the size of the pupil when the exam begins, using a pupillometer. Direct comparisons of pupil size will be made with the pupillometer held at the outer canthus of the right eye.

3.3.1 LENS EXAMINATION: The examination of the lens will be first carried out using direct and retroillumination with the slit-lamp at low magnification. A lenticular change will appear as a hard white or grey obstruction to the normal transparency of the lens. Presence of waterclefts, spokes, and lamellar separations (sometimes called early or presenile lens changes) will not be recorded. Also not Included as lens changes will be Mftttendorf dots, small axial embryonal sutural opacities or other small punctate dot-like opacities.

Aphakla refers to any lens that has been operated upon, even If lens remnants are present. For the purpose of this study, It also Includes a tubluxated or dislocated lens.

The lens examination wlll be considered adequate if at least two-thirds of the anterior surface can be visualized by angling either the examinee's eyes or the slit-lamp direction.

If aphakia is noted, record the year of cataract surgery.

If IOL is noted, record the type. If IOL has been removed, record the year of removal.

3.3.2 LENS CHANGES

3.3.2.1 DECREASED NUCLEAR LUCENCY: These changes are seen in direct illumination as a diffuse increase in the optical density of the lens nucleus (sclerosis) when compared to the adjacent cortex with color varying from faintly brown to black and interrupting the slit beam.

The nucleus is examined with a thin (0.1mm) slit beam of 8 to 9mm in height set at an incident angle of 30°. The slit passes through the anatomic center of the lens (the embryonic nucleus) and the clarity of the optical section of the nucleus compared to the standard photographs and graded accordingly. The standard photographs are 35mm transparencies that are viewed in a hand held, battery operated slide viewer. Grade these opacities using the standard photos. 0 if < STD1; 1 if ≥ STD 1, < STD2; 2 if ≥ STD 2, < STD 3; 3 if > STD 3.

3.3.2.2 CORTICAL CUNEIFORM LENS CHANGES: These changes 'are seen in retroillumination as large white flat radial wedge-shaped opacities located peripherally in the cortex of the lens and directed centrally. They can be seen well in retroillumination as contrasted with spokes. These opacities may be continuous with waterclefts of lamellar separation.

The cortex is examined using retroillumination with the slit beam relatively wide (0.5 to 1mm) and short (4 x 5mm) In height. The slit beam is angled through first one side of the pupil and then the other so that the entire cortex can be examined In clear retroilluminatlon. The focus of the slit-lamp must be altered so that both the anterior and posterior cortical regions are each examined In clear focus.

The presence or absence of cortical wedges, or spokes, or other cortical opacities is then assessed. If cortical opacities are present, they are graded by estimating the proportion of the total circumference of the lens occupied by the combined cortical opacities as if they were adjacent. This is best done by visually dividing the pupillary area first into quadrants and then into eighths. The circumferential extent of each opacity is assessed and then the combined circumference of all opacities estimated. Grade these opacities based on the combined circumferential extent: 0 = absent; 1 if < 1/8; 2 if $\geq$ 1/8, < 1/4; 3 if $\geq$ 1/4, < 1/2; 4 if $\geq$ 1/2.

3.3.2.3 POSTERIOR SUBCAPSULAR LENS CHANGES: Vacuolar or granular-appearing opacity located subcapsularlyin the posterior axial region. It frequently has a saucer-like shape. Vacuoles appearing in the posterior subcapsular area will be designated as posterior subcapsular senile lens changes. These opacities will be quantitated by measuring the vertical and horizontal dimension of the posterior subcapsular plaque in retroillumination using the slit size calibration of the slit lamp. If these changes are oriented in an oblique direction, the maximum length and width are measured by tilting the slit lamp beam.

3.3.2.4 VACUOLES: These are seen in retroillumination and are recorded as present or absent.

3.3.3 MACULAR EXAMINATION: The nacula is defined, for the purpose of this study, as the area one disc in radius surrounding the foveola. The fovea Is the area about 700 microns in diameter centered on the foveola corresponding to the vascular free zone of the posterior fundus. The nacula and posterior pole should be examined first using the direct ophthalmoscope. Only if an adequate view has not been obtained will the Indirect ophthalmoscope or the Volk 90D Lens be used. In additlon, when examiner 2

does the photography, he/she will check the findings of the first examiner; values recorded on the data form are consensus values.

3.3.3.1 ADEQUACY: The macular examination will be considered adequate if performed through a dilated pupil and all features of the macula and posterior pole are seen clearly with the direct ophthalmoscope or Volk Lens. The examiner shall note the following:

3.3.3.2 FOVEAL REFLEX: Fovea1 reflex will be evaluated by choosing the best description of the condition: none - no fovea1 reflex is evident; questionable - some light reflexion but no confined to a single point on the fovea; present but abnormal - anatomical fovea present with irregular contours and borders; present and normal - anatomical fovea1 containing perfect point on the center of the fovear.

3.3.3.3 MACULAR NEVI: Areas of pigmentation thought to be nevi found within one disc diameter of the center of the fovea are recorded if present. If present, these areas of pigmentation will be ignored in responding to subsequent questions.

3.3.3.4 NON-DRUSEN MACULAR PIGMENT DISTURBANCE: Includes any changes in the regularity of the pigment epithelium (atrophy, migration, mottling, granularity) from any cause if it occurs within the defined area of the macula ignoring changes that are thought to be discrete drusen. Great care must be taken to distinguish multiple small areas of pigment atrophy and multiple drusen. Pigmentary changes would also include conditions such as chorioretinitis, traumatic naculopathy, exudative maculopathy, and others. Aging changes of the macular pigment epithelium are often characterized by either a slight gralniness or a decrease in the density of pigmentation. Occasionally, the aged macula will be void of clinically apparent pigment. Do not classify these latter aging changes as pigment disturbance.

The following descriptions correspond to photographs used in the original Framingham Eye Study:

0 - "No" pigment disturbance. Although there fs no foveal reflex fn this fundus and a suggestion of granularfty in the superior temporal segment of the macula, there fs essentially no pigmentary change. Any eye with thfs fundus picture should be reported as pigment disturbance "none."

1 - "Questionable" - pigment disturbance. The slight mottling and suggestion of defect in the pigment epithelium should not be called "present."

2 - "Present" - 'subtle pfgment disturbance. The defects in retinal pigment epithelium are clear and distinct, but are minimal at best. "Subtle" defect refers to macular pigment changes (mottling, granularity, atrophy, migration) that are present but not very noticeable. The defects would not be usually apparent at first observation but visualized after closer scrutiny of the macula.

3 - "Present" - obvious pfgment disturbance. The pigment disturbance can be easfly visualized. Clumps of pigment involving either hypo- or hyper-changes. There would be no question about the certainty of macular changes being present.

4 - "Present" - severe pigment disturbance. The pigment disturbance is so marked that a recognizable macula is no longer observed. Large clumping and areas of atrophy.

Categorize all questionable, subtle, obvious, or severe pigment changes as to location, i.e., whether the plgment changes involve the fovea.

If there is geographic atrophy of the pigment, record the amount of disc areas Involved.

3.3.3.5 MACULAR DRUSEN: Drusen are located deep In the retina at Bruch's membrane level, and displace pigment epithelium. They can vary from

what appears simply as defects in the pigment epithelium to small yellow collofd-like dots, to larger yellow softer lesions.

The following method will be used to classify the presence and size of macular drusen:

0 - "None" - No evidence of macular drusen.

1 - 'Questionable" - Slight mottling of the macula (similar to "questionable" pigment disturbance) only there is a suspicion that the defects are tiny drusen rather than pigment disturbances alone.

2 - "Present" - fovea spared or questionably involved. Definite drusen are present in the posterior pole, but are at most questionable within the area designated as fovea.

3 - 'Present" - fovea involved. The fovea1 area has definite drusen.

"Questionable" drusen would be similar to the defects seen in the photograph "questionable macular pigment disturbance. If "present' or "questionable" drusen are observed, categorize as to location: 2 = "macular" (if < 1 disc diameter from center of 'fovea) or 3 = "peripheral" (if 1 or more disc diameters from center of fovea, but still within the arcades) or 4 = "both." "Peripheral" means Inside posterior pole (as in macular pigment disturbance). If "present", estimate the total number In the macula. When only a few drusen are observed, count them to determine if more or less than ten. Estimate whether there are more than 10 and less than 100, or more than 100.

*Differentiate the drusen by extent of soft and hard drusen. Hard drusen are hard and round (oval) with definite edges appearing as discrete lesions easily distinguishable from normal retina. They are usually 100-150 microns in size or smaller. There is some depth but are not markedly elevated. Soft drusen are larger In slze (150+ microns). Their borders may not be well

defined and they may blend with surrounding tissue (they are not as easily distinguishable from the retina). Evaluate the presence of soft drusen and estimate the percentage of soft drusen: less than 20%, between 20 and 60%, or greater than 60%.

3.3.3.6 PIGMENT EPITHELIAL DETACHMENT: The macula should also be observed for the presence of round (oval) shape dome-like elevations in the retina pigment epithelium. They may vary in size from less than 1/2 disc area to cover the entire posterior pole. Record as "questionable" if it appears that the macula might be elevated and "present" if the macula is obviously elevated noting the involvement of fovea.

3.3.3.7 NEUROSENSORY SEROUS RETINAL ELEVATION: This is the presence of fluid between the retina and underlying pigment epithelium causing dome-like elevations of the retina. These elevations may be associated with pigment epithelial detachment. Record as "questionable" if it appears that the macula might be elevated and "present" if the macula is obviously elevated nothing the involvement of the fovea.

3.3.3.8 SUBRETINAL HEMORRHAGE: This is the presence of blood efther underneath an elevated neurosensory retinal elevation or pigment epithelial detachment. Blood between the neurosensory retina and R.P.E. appears red whereas blood under the R.P.E. may be invisible if the R.P.E. or neurosensory retina is detached, or may appear as a red or green discoloration. Subretinal blood is almost always associated with a subretinal neovascular membrane which often has a gray-green discoloration and may be associated with exudate deposits. Record as "questionable" If It appears that the hemorrhage night be present and "present" if the hemorrhage definitely is present noting the Involvement of the fovea.

3.3.4 OTHER OPACITIES: The presence of other ocular opacities or other factors that night reduce visual acuity should be recorded.

3.3.5 FUNDUS PHOTOGRAPHY: Stereo retroillumination photos of the lens and stereo photographs centered on the disc (field 1) and macula (field 2) will be obtained.

Stereo fundus photography is carried out using the Zeiss fundus camera modified as follows:

A. Fundus camera is moved backwards (away from the patient) on its base sufficiently so that its center of rotation corresponds to the pupil of the patient's eye.

B. No. 7 aperture (14 mm diameter) in recoss disk modified by adding a central 6 mm dfameter opaque disk (referred to as "black dot" by Zeiss). It is further recommended, but not required, that Kodak Wratten filter #81A be added to this aperture.

C. Power supply modified to allow recharging within one to two seconds.

D. Opaque cone removed from film carrier to allow use of entire image.

The technique described by Allen is used to obtain stereoscopic photos of field 1 and field 2.

The most common error in funds photography is poor focus, which can be avoided if the photographer develops a constant awareness of the need to keep the cross hairs in the ocular of the camera in sharp focus by adjusting the ocular as often as necessary. No specific electronic flash setting is specified since this will vary with the model of camera used, but is most frequently used at 120 w. (flash setting 12).

3.3.5.1 PUPILLARY DILATION

Adequate dilation of the pupil is important to permit good quality stereo photography. Sufficient time should be allowed for dilation to at

least 6 mm, repeating drops, if necessary, to achieve and maintain a pupil of at least this size during photography.

3.3.5.2 COLOR PHOTOGRAPHY

Field 1, 2, lens

Fields 1 and 2 of the fundus are defined below for both the right and left eyes. There are two cross hairs in the camera ocular, one vertical and the other horizontal.

Field 1 - Disc

Center of optic disc at intersection of cross hairs in ocular.

Field 2 - Macula

Cross hairs 1/2 disc diameter temporal to the center of the fovea to throw any central artifact off the fovea.

"Lens" Photograph

A single stereo pair of photographs of the lens should be taken in addition to those required of the disc and macula.

In order to take the lens photographs it is necessary to use the +16/+33 diopter setting on the auxiliary plus lens system of the camera. "The small white knob on the right side of the Zeiss Unit is turned until the correct number (+16/+33) appears at the dot. In order to standardize the magnification of these photographs, the following procedure should be used:

A. The film-to-lens distance of the camera is increased to its maximum, by turning the large focusing knob so that its upper aspect moves toward the patient. Turn the knob in this direction as far as It will go.

8. The patient's head rest is moved away from the camera until the iris is In crisp focus (approximately 1 1/2 inches further away than when adjusted for taking photographs of the fundus). It is acceptable to move the patient

slightly further away, so that the focusing knob may be used for fine adjustment of focus if the photographer wishes.

C. The patient is asked to open his/her eyes very widely, or the lids should be gently retracted if necessary, so that the entire cornea is visible.

D. The photograph is taken.

3.3.5.3 Film Processing, Mounting, and Labeling

Kodachrome 25 Daylight film is used and may be processed in routine fashion at any Eastman Kodak Processing Laboratory. It is important that the processing laboratory correctly orient each transparency in the readymount and correctly number the readymounts. Transparencies processed by Kodak are in the proper postion when the frame number is visible and right side up.

The transparencies returned from the processing laboratory are mounted in standard cardboard 2 x 2 readymounts. Each readymount is identified on the bottom of the cardboard frame with a label on which is written or printed the patient identification number, the eye (right and left), and the date at which the photographs were taken.

The originals of each patient set are sent to the Photographic Reading Center in Madison, Wisconsin. A copy of each set is maintained at the Framingham Eye Study. Copies are obtained by taking duplicate sets.

The mounted and labeled transparencies should be placed in 9 x 11 inch transparent plastic sheets containing 20 pockets per sheet.

Slides should be placed In plastic sheets in anatomic position, as illustrated below, with disc nasal'and macula temporal as one would view an eye. The lens photos should be placed directly below the macular photos of that eye.

The Identification labels are completed and attached to the front of the plastic sheets. The label includes the patient identification number, name,

and date the photographs were taken.

Photographs are mailed to the Reading Center weekly. Each batch is accompanied by a transmittal form listing the content and quality assessment;

3.3.6 CORNEA1 ABRASION: Inspect the surface of the cornea for an abrasion. If a definite cornea1 abrasion exists, a determination should be made if treatment is necessary and a treatment plan implemented.

3.3.7 EXAMINER: Record the code number for the examiner performing the various sections of the examination.

3.3.8 SPECIAL PATIENT CARE PROCEDURES

A log is maintained listing persons with IOP above 21 mm Hg, pigment epithelial detachment, neurosensory retinal elevation, subretinal hemorrhage, or suspicion of subretinal vessels, cornea1 abrasion, or other pathology. If there is some pathology observed at the time of the exam which, in the examiner's opinion, warrants attention, the patient is questioned, without alarming him/her, as to whether he/she is being followed by an M.D. If he/she is being followed, a note is made in the record and the photos are reviewed in the normal manner. If not, the photos are reviewed as soon as they are processed. Review of photos and ophthalmic forms is performed with Dr. Rand every two weeks and proper action is taken (letter to M.D., O.D., and/or patient). A list of all persons not dilated is also kept and these patients are discussed at this time.

update 1/12/88
by Group Op.

CHAPTER 4. Data Management

4.1 EXAMINATION DATA

4.1.1 DATA ENTRY

4.1.1.1 INITIAL DATA ENTRY

The lead examiner enters data weekly onto floppy disks on an IBM PC/XT compativle canputer, using data entry software written in dBASE-III by Group Operations. Data entry occurs through the use of formatted screens that closely mimic the layout and content of the exanination form. Field edits are applied at the time of data entry; if a value is flagged as invalid, the operator re-enters the data item before proceeding with the rest of the form. The examiner maintains a record of the ID nunber of all forms keyed, in the order entered.

4.1.1.2 REPLICATE DATA ENTRY AND VERIFICATION

The first three diskettes of data transmitted to Group Operations were accompanied by a copy of the paper data form, which was used by a data entry service bureau to re-key these first 352 forms. Ebr these forms, the initial and replicate entries are compared by means of a SAS program written by Group Operations. Discrepancies are checked against the data forms and the original

copy of the keyed data is updated by *Group* Operations, as needed.

Beyond the first *three* sets of data, verification is carried out by means of full replicate data entry by a part-time clerical support member of the Framingham staff. After the full set of forms has been rekeyed (in the sane order as the initial entry) a program is run which compares the two versions of the data and reports any discrepancies. This program, written in dBASE-III, produces a printed report of the ID number, data fields, and discrepant values for any record with differences between the original and verification copies of the keyed data. The operator (either lead examiner or clerical staff member) reviews the printed report, comparing the discrepant data entries to the actual data form. If the initial copy is *correct,* this is noted on the verification report. If the initial copy of the data is in *error, the* correct data value is noted on the verification report. After reviewing all discrepancies for one diskette of data, all necessary changes are made in the initial copy of the keyed data using the data entry proqram in **"update" mode.**

4.1.2 WTA TRANSMISSION

Approximately once a month, the verified and corrected initial copy of the keyed data is transmitted electronically to the NIH Division of Computer Research and Technology (DCRT) computer facility. Data accumulated since the last transmittal is translated from the dBASE-111 file into a fixed-format EBCDIC character file and then transmitted by telephone to the NIH computer facility by means of the KERMIT telecommunications utility. The transmitted data resides as a WYLBUR data set under the Framingham account on the NIH computer. At the time of transmittal, Group Operations is notified, via WYLBUR MAIL, of the name of

the WYLBUR data set containing the new data. The diskette containing the data sent to Group Operations is maintained at the Framingham site.

4.1.4 DATA EDITING AND CORRECTION

Keyed and verified data is edited by Group Operations, using a SAS program written for this purpose. The edit program checks for correct identifiers, through comparison to a master record of subjects eligible for the FES-II study. It then checks for consistency across all items of information with specifiable logical relationships. *Errors* identified by the edit program are printed out and sent to Framingham for resolution. The error report is formatted in a way that provides a clear indication of the data that was keyed, the nature of the error, and a space for the Framingham staff to indicate what updates are to be made to correct the *errors.* The Framingham staff makes a photocopy of the correction documents and files them with the subjects' original examination forms, as a record of final data for each subject. The original correction documents are mailed to *Group* Operations where they are used to update the master copy of the FES-II data file.

4.1.5 FILING AND STORAGE OF DATA FORMS

Data forms are filed in order by ID nunber after data entry is complete. A facsimile of the data form, showing all items and data values for each subject, is computer generated in triplicate by Group Operations after all data editing and updating has been completed. One copy of the form facsimile is placed in the FES file for that subject, one copy is placed in the FHS patient file, and the third copy is maintained at Group Operations.

4.1.6 SUMMARY LETTERS

Upon receipt of new data from the Eye Clinic, Group Operations produces a canputer-qenerated letter summarizing all information obtained fran each patient's examination. Three copies of these letters are produced and sent to the Eye Clinic for distribution: one copy for the FES file, one copy for the FHS patient file, and one copy which' is then sent to the patient's ophthalmic care provider or qeneral physician.

4.1.7 SPECIAL LETTERS

As each new batch of data is received from the exanination site, a special report is computer-qenerated for any subject whose exanination data indicated possible presence of a clinically significant condition. Reports are sent in triplicate to the Framinham site, for referral to the relevant ophthalmic care providers.

4.1.8 REVIEW, LABELING, MOUNTING, ANd TRANSMITTAL OF PHOTOGRAPHS

Processed photographs (slides) for each subject are reviewed for quality and for complete sets. The best available set of photographs for each subject are individually labeled and then mounted into transparent slide storage pages as described previously. These are sent periodically to the Photographic Reading Center, with an accompanying transmittal sheet. A duplicate set of slides, of identical or next-best qual ity, is labeled and mounted in the same manner as the original set. This duplicate set is maintained in the patient's file at the Eye Qinic.

4.2 PHOTOGRAPHIC DATA

4.2.1 WTA TRANSMITTAL

Once a month, photographic grading data forms are mailed from the photo reading center to the data management center (Group Operations, Inc.). Grading forms are sent in sets of four forms per patient visit, a "set" consisting of two complete gradings of each of two eyes. A copy of each grading form is maintained on file at the photo grading center.

4.2.2 LOGGING AND BATCHING OF FORMS

Upon receipt at *Group* Operations, a data clerk reviews the contents of each package of photographic data forms, separates the forms by visit (1 *or* 2), and organizes the forms into batches for further processing. Within each batch, forms are sorted by ID nunber, eye, and grader. Forms for each patient visit are then checked for the presence of complete sets of two eyes and two graders. Sets of forms are logged onto batch log sheets, and the nunber of forms is recorded on a cover sheet *for* each batch.

4.2.3 KEYING OF PHOTOGRAPHIC DATA FORMS

Batches of forms are picked up by a data entry service which performs entry and full verification of all data from the photographic grading forms. Keyed data is returned to Group Operations on magnetic tape, along with the original data forms.

Upon receipt at Group Operations, the keyed data file is transferred to disk storage at the NIH computer facility. Record counts are checked and each record is tagged with its batch nunber.

4.2.4 ADJUDICATION OF PHOTOGRAPHIC GRADING

Adjudication of discrepancies between qraders occurs through several steps, as described below.

4.2.4.1 RE-GRADING OF DISCREPANCIES

First, a program is run which identifies discrepancies of more than one value on the grading scale, for each sub-field of each lesion. A computer-generated report is produced which contains identifying information and a label for each lesion and subfield for which discrepant qradings have occurred; original gradings are not reported, so that re-grading is 'blind" to all previous information. The report is produced for each of the two graders who originally graded the photographs.

Each *grader* regrades all relevant fields and indicates the grad ing values on the re-qrading report. A copy of this report is maintained in the file at tie photo reading center; the origignal is sent to Group Operations for updating of the data base.

4.2.4.2 ADJUDICATION OF RE-GRADED PHOTOGRAPHS

Upon receipt at Group Operations, data for the re-graded lesions and sub-fields

is applied to the original photo data records through an interactive SAS update procedure. Following updating, the adjudication *program* is then re-run. Any eye for which a discrepancy still remains after re-grading results in the generation of data reports to be used for adjudication. These reports consist of a printout of identifiers and lesions/sub-fields to be adjudicated (exactly like the blind re-grading form described above), plus a report form which contains all relevant information fran previous qradings.

Ad j&cation is carried out by means of a third, independent and blind grading of the lesions/sub-fields at issue. After re-grading, the ad j ud icator records the resulting values on the re-grading form and then refers to the adjudication report to compare this third qrading to the two previous ones. A decision is made which resoslves the discrepancy, and the adjudicated data value is indicated on the adjudication report. This report is then sent to Group Operations for adjudicated values to be incorporated into each original grading record.

4.2.5 DATA EDITING

Following identification, re-grading, adjudication, and updating of any discrepant qradings, photographic data is submitted to a SAS proqran which performs complete edit checks for the presence and consistency of data values, according to a detailed edit specification document which has been developed by Group Operations and reviewed by the photographic readinq center.

The edit proqram results in a full report of all data values for any form with *errors.* This report parallels the original data form and includes an indicator

of each field in question plus a full statement of the nature of the error which has been detected. Each field in question has next to it a space for providing corrected data values. A copy of the edit report is maintained at the photographic reading center, and the original is sent to Group Operations. Corrected data is entered into the data base using an interactive SAS update procedure .

4.2.6 CREATION CF A FINAL DATA FILE FOR PHOTOGRAPHIC DATA

Following adjudication and editing of the two qradings for each eye at a given visit, a data record is constructed which contains a final data value for each lesion and sub-field. values are from the first qrading form if identical, are computed as averages (mid-pints) of the two gradings if different by one scale value, and are replaced with the adjudicated data value if gradings differ by more than one scale value. A complete trailer of processing steps and outcomes is attached to each photo qrading record in the final, analyzable data file.

4.2.7 MONITORING AND REPORTING ON DATA FLOW

As the data management center for this study, Group Operations maintains a central record of the status of patients being contacted for Visit 2 examinations. Periodic *reports* are produced for the Project Officer , summarizing *the* numbers of patients exanined, remaining to be exanined, and not available for exanination.

Group Operations also maintains a record of the status of data records through re-grading, adjudication, editing, and updating. This record can be used to

summarize project status as well as to report on individual examination or photo grading forms.

APPENDIX A

Clinical Examination Form

NEI - FES - EX1

I [ ][.][ ] D

EYE EXAMINATION

Name _____ Date of birth MO [ ][ ] DY [ ][ ] YEAR [ ][ ][ ][ ]

Date of examination MO [ ][ ] DY [ ][ ] YEAR [1][9][8][ ]

Subject's ophthalmologist/optometrist/physician:

Name _____

Address _____

Summary sent on **(date)** _____

PART I _____

Place of examination: cl
(1=FES clinic; **2=local; 3=elsewhere)**

1. Loss of an eye <includes anucleation and phthisis **bulbi):** ..... OD [ ] OS [ ]
(0=Eye present, **1=Eye** absent)

2. Visual acuity **(VA)** and Refraction: (code all **8's** if not applicable, all **9's** if unknown)

a.1 VA with "walk-in" correction. by refractometer, if possible: . . . OD [ ][ ]/[ ][ ][ ]+[ ] OS [ ][ ]/[ ][ ][ ]+[ ]

a.2 Done **by: (0=refractometer, 1=projected** VA **chart)** II

a.3 Walk-in" correction : **0 nothing**
1 spectacles
2 contact lens
8 eye absent
9 unknown

OD [ ] OS [ ]

b.1 Refractive **error,** by refractometer if **possible:**
(Use trial lenses if refractometer cannot be done or if **unreliable** for this subject)

	SPHERE	CYLINDER	AXIS
, right • ya	± [ ][ ]•[ ][ ]	± [ ][ ]•[ ][ ]	[ ][ ][ ]
left • yo	± [ ][ ]•[ ][ ]	± [ ][ ]•[ ][ ]	[ ][ ][ ]

b.2 **Done** by: **(0=refractometer, 1=trial lenses)** 0

c. **Best corrected** VA **(after refraction):** OD [ ][ ]/[ ][ ][ ]+[ ] OS [ ][ ]/[ ][ ][ ]+[ ]

NEI - FES - EX2

I[ ][.][ ]D .

	OD	OS
3. a. Angle **depth** A **(0=Suspicious, 1=Adequate):**	☐	☐

If **Angle** depth A = 1 ---------> Go to question 4

If Angle depth A = **0,** the patient should have a slit-lamp **exam** before dilation and the following question answered:

	OD	OS
b. Angle depth **B,** by slit **lamp:** ..... **(0=Do** NOT dilate; **2=Adequate,** dilate; **7=Not** applicable)	☐	☐

	OD	OS
4. **Intraocular** pressure before drops: . ..*.....*..... a mm **Hg.**		☐☐ mm Ho.
(88=Eye absent, **99=Unknown)**		

	OD	OS
5. **Iris color:** ..... **(1=Brown, 2=Mixed, 3=Blue, 8=Eye** absent, **9=Unknown)**	II	☐

Dilating drops instilled at **(time):** _____

PART II

6. Pupil **dilation:** **0** adequate
2 inadequate
3 dilation contraindicated
8 eye absent
9 unknown

OD ☐ **OS** ☐

a. Pupil size **(mm):** ..... OD ☐ **OS** ☐

SLIT LAMP EXAM:

7. Lens examination: 0 adequate
2 inadequate
6 aphakia with IOL
7 aphakia without IOL
8 eye absent
9 unknown

OD cl ☐ **OS** ☐

If non-aphakic ------> Go to question **8**

If **aphakic:**

a. Year of cataract surgery: ..... OD **19**☐☐ **OS** **19**☐☐

b. **If** IOL is present: **0** no IOL
1 **ant.chamber**
2 post. chamber
3 iris clip
8 eye absent
9 unknown

OD ☐ **OS** ☐

c. Has IOL been removed? 0=Yes, 1=No, 7=N.A. ☒ ☐

d. If **IOL** not **present,** but removed, year removed: OD **19**☐☐ **OS** **19**☐☐

8. Lens changes: **(8=Eye** absent, **9=Unknown)**

a. Decreased nuclear **lucency:** ..... OD ☐ OS ☐
CO: **<** Std **1)** **(1:>=** Std **1, <** Std **2)**
(2: >= Std 2, **<** Std **3)** **(3: >=** Std **3)**

b. Cortical cuneiform lens **changes:** ..... OD ☐ OS ☐
(0:Absent) **(1:Present < 1/8)** **(2: >= 1/8, < 1/4)**
(3: >= 1/4, < 1/2) **(4: >= 1/2)**

c. Posterior rubcapsular lens **changes:** ..... OD ☐×☐ **OS** ☐×☐
(Vertical x Horizontal dimensions, **in mm.)**
(Use 8x8 for • yo ● bsont, 9x9 for unknown1

d. **Vacuoles (0=Absent, 2=Present):** . . . . . OD ☐ OS cl

e. Other **(specify):** OD_____ **OS**_____

Macular Examination:'

9. Adequacy:
0 adequate
1 borderline adequate
2 inadequate
8 eye absent
9 unknown
OD OS
II

10. Ophthalmoscope used:
2 direct or Volk or camera only
3 indirect only
4 both direct and indirect
8 eye absent
9 unknown
OD OS
cl

4

11. Macular nevir .....
(0=Absent, 1=Questionable, 2=Present, 8=Eye absent, 9=Unknown)
OD OS
II

12. Fovea1 reflex:
0 none
1 questionable
2 present, but abnormal
3 present and normal
8 eye absent
9 unknown
OD OS
II

13. Non-drusen macular pigment disturbance:
0 none
1 questionable
2 present, subtle
3 present, obvious
4 present, severe
8 eye absent
9 unknown
OD OS
II

If no macular pigment disturbance -----> Go to question 14

If macular pigment disturbance:

a. Location:
0 fovea not involved
1 fovea questionably involved
2 fovea definitely involved
fovea entirely destroyed
3 not applicable
8 eye absent
9 unknown
OD OS
cl

If fovea not involved or fovea entirely destroyed -----> Go to question 14

b. If fovea questionably or definitely involved8

1 increased granularity
2 pigment clumping
3 pigment ● trophy
4 both
7 not applicable
8 eye ● bsent
9 unknown
OD OS

If increased granularity or pigment clumping only -----> Go to question 14

If pigment atrophy, or pigment atrophy and pigment clumping:

c. Geographic ● trophyr
2 < 1/2 disc area
3 < 1 disc area
4 >= 1 disc ● rea
7 not applicable
8 eye ● bsent
9 unknown
OD OS

14. Macular drusen: 0 absent
1 questionable
2 present, fovea spared or questionably involved
3 present, fovea definitely involved
8 eye absent
9 unknown

OD ☐ OS ☐

If drusen absent -----> Go to question 15

If drusen questionable or present:

a. location: 2 macular
3 peripheral
4 both macular and peripheral
8 eye absent, or no drusen, or unknown if drusen
9 location unknown

OD II OS ☐

b. Estimated number: 2 1-9
3 10-99
4 100 or more
8 eye absent or unknown if drusen
9 number unknown

OD ☐ OS ☐

c. Type: 0 no soft drusen
1 questionable soft drusen
2 soft drusen but < 20%
3 soft drusen but < 60%
4 soft drusen but >= 60%
8 eye absent
9 unknown

OD cl OS ☐

15. Pigment ● pithelial detachment:

0 absent
1 questionable
2 present, fovea spared or questionably involved
3 present, fovea definitely involved
8 eye absent
9 unknown

OD ☐ OS ☐

16. Neurosensory serous retinal elevation:

0 absent
1 questionable
2 present, fovea spared or questionably involved
3 present, fovea definitely involved
8 eye absent
9 unknown

OD cl OS ☐

17. Subretinal hemorrhage:

0 absent
1 questionable
2 present, fovea spared or questionably involved
3 present, fovea definitely involved
8 eye absent
9 unknown

OD ☐ OS ☐

18. Do other opacities of the ocular media exist which may reduce visual acuity ?

OD ☐ OS ☐

0 No
1 Yes: cornea
2 Yes: vitreous
3 Yes: other (Specify _____)
8 Eye absent
9 Unknown

NEI - FES - EX6

[ ][ ][ ][ ] I.D.

PHOTOGRAPHY:

19. Photography done ? 0 = No <Reason _____) cl

1 = Yes, inadequate <Reason _____)

2 = Yes, adequate

a. Is call-back for Photography recommended ? (0=No, 1=Yes) cl

EXAMINATION COMPLETION Cat Slit Lamp):

OD OS

20. Exit intraocular pressure (88=Eye absent, 99=Unknown): [ ][ ] mm Hg. [ ][ ] mm Ha.

Cornea1 abrasion ? (not coded)

OD _____

OS _____

21. Examiners: Part I ..... [ ]

Part II ..... [ ]

Photography ..... a

1 Mark Roseman
2 Peggy Stockman
3 Jeffrey Sol
4 Lawrence Rand
5 Frederick Ferris
6 Other (_____)
9 <Photography not done)

22. Was patient asked to contact his doctor? [ ]

Y=Yes N=No

9/5/86