

# **Complications of Age-related Macular Degeneration Prevention Trial (CAPT)**

## **Manual of Operations**

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# CAPT MANUAL OF OPERATIONS

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# CHAPTER 1

## BACKGROUND AND DEVELOPMENT

### 1.1. OBJECTIVE OF THE TRIAL

Age-related macular degeneration (AMD) is the leading cause of blindness among Americans aged 65 and over and among the older populations of other Western countries. Most, approximately 90%, of the blindness is attributable to the neovascular form of AMD. The remainder is attributable to pigment epithelial detachment or geographic atrophy. The Macular Photocoagulation Study (MPS) has shown that laser photocoagulation is beneficial in reducing the frequency and severity of visual loss in eyes with neovascular AMD. However, the average visual acuity of treated eyes is 20/250 - 20/320 and the majority of neovascular lesions are not amenable to laser treatment. In early 2000, the FDA approved photodynamic therapy (PDT) with verteporfin for the treatment of CNV. PDT with verteporfin, when used with patients with subfoveal lesions with a predominantly "classic" (versus occult) pattern of fluorescence on fluorescein angiography, can reduce the risk of moderate vision loss for at least one year (Treatment of Age-related Macular Degeneration with Photodynamic Therapy Study Group, 1999). Although this new treatment does enlarge the subset of lesions amenable to some form of treatment, more than half of all lesions are not eligible for PDT because they have a predominantly occult pattern of fluorescence on angiography or have too much blood. There are no other proven treatments for choroidal neovascularization (CNV) secondary to AMD. Likewise, there are no proven treatments for pigment epithelial detachments or geographic atrophy.

Prevention of vision loss from the advanced forms of AMD would have profound public health implications. An intervention that reduced the risk of developing CNV by 30% in eyes of people with bilateral large drusen could **halve** the rate of bilateral blindness from AMD. Since the 1970's, investigations have reported consistently that laser photocoagulation causes high risk drusen (deposits under the retinal pigment epithelium) to disappear. Results of the effect of laser treatment on prevention of the late forms of AMD and on vision loss have been less consistent and have been based on relatively small numbers.

The large segment of the population that might benefit, or be harmed, by prophylactic laser treatment mandates a carefully planned and executed clinical trial. The Complications of Age-related Macular Degeneration Prevention Trial (CAPT) has been designed to assess the safety and effectiveness of laser treatment in preventing loss of visual function among patients with bilateral large drusen.

The specific aim of this multi-center, randomized clinical trial is to evaluate laser treatment in comparison to observation within patients having high risk drusen in both eyes. Laser treatment will be evaluated using the following criteria:

- Change in visual acuity (primary criterion);
- Incidence of CNV, pigment epithelial detachment, and geographic atrophy;
- Change in contrast threshold;
- Change in critical print size for reading.

In addition, participating patients will be described using a widely used measure of vision-specific quality of life.

## 1.2. CLINICAL AND HISTOPATHOLOGIC FEATURES OF AMD

Age-related macular degeneration is an ocular condition characterized in the early stage by drusen and pigmentary changes in the macular area, and degeneration of the retinal pigment epithelium (RPE). The late stage of AMD is characterized by geographic atrophy, RPE detachment, CNV, and disciform scar. Only the late stage of macular degeneration results in moderate and severe losses in visual function.

Various types of drusen can be differentiated clinically and photographically based on number, size, distinctness of borders, thickness, and confluence (Gass, 1973; Gregor, 1977; Bressler, 1989; Klein, 1991). Small (<64 microns) drusen with sharp, well demarcated borders are often termed **hard** drusen. On histologic examination, these drusen appear to be localized accumulations of hyaline material with or without thin and depigmented overlying RPE or individual depigmented RPE cells with an accumulation of lipid (Sarks, 1980; Green, 1985; Feeney-Burns, 1985; Bressler, 1994). More than 95% of adults over the age of 41 years have at least one hard drusen in one or both eyes (Klein, 1992). Hard drusen have not been associated strongly with the later, vision threatening forms of macular degeneration.

Drusen that are >63 microns typically have poorly demarcated boundaries and/or a thick appearance. Thus, the terms **large** drusen and **soft** drusen are sometimes used interchangeably, although large hard drusen and small soft drusen are observed occasionally (Klein, 1991; Bressler, 1990). On histologic examination, areas corresponding to soft drusen have localized RPE detachment and either basal laminar deposit [widely spaced collagen and minor deposits of other material located between the plasma membrane of the RPE cell and the basement membrane] or basal linear deposit [vesicular and granular electron dense, lipid rich material external to the basement membrane of the RPE] (Green, 1993; Bressler, 1994; Sarks, 1994). The presence of soft drusen has been associated with a diffuse thickening of the inner aspect of Bruch's membrane throughout large areas of the macula (Feeney-Burns, 1985; Pauleikhoff, 1990). The prevalence and incidence of soft drusen increases steadily with age (Klein, 1992; 1997). In the Beaver Dam Eye Study, prevalence increased from 7% among those aged 43-54 years to 44% among those age 75 and older. In contrast to hard drusen, soft drusen have been repeatedly associated with increased risk of the vision threatening forms of macular degeneration (Gass, 1973; Gragoudas, 1976; Gregor, 1977; Strahlman, 1983; Smiddy, 1984; Bressler, 1990; Klein, 1997; MPS Group, 1997).

### 1.3. DEVELOPMENT OF CNV

New vessels, which originate from the choroid and grow through breaks in Bruch's membrane and under the RPE, result in severe loss of visual function. The pathogenesis of CNV is not known. Recently, there has been great interest in polypeptide growth factor stimulation of ocular angiogenesis (D'Amore, 1994; Adamis, 1994). It may be that the delicate balance of polypeptide angiopromoters and angioinhibitors is tipped in favor of neovascularization by the diffuse thickening of Bruch's membrane which in turn alters the relationship of the retinal pigment epithelium and the underlying choroidal vasculature. Retinal pigment epithelial cells harbor a variety of growth factors that promote the growth and development of CNV and are easily implicated because of their proximity to choroidal vessels. In addition, monocyte inflammatory cells, known to harbor cytokines and growth factors, have been identified in eyes with CNV and may be recruited to areas with abnormal basement membrane. They may even participate in the disruption of basement membranes thereby promoting ingrowth of CNV (Penfold, 1985). Examinations of surgical specimens excised from patients with CNV have provided immunohistopathologic evidence that such growth factors as basic fibroblastic growth factor (BFGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF beta) are bystanders, if not participants, in the processes of CNV (Amin, 1994; Reddy, 1995; Kvanta, 1996). Thus, interventions that affect growth factors may be particularly fruitful in controlling the development and progression of CNV.

Some of the additional hypotheses for the development of CNV are 1) that the physical barrier to blood vessel growth presented by Bruch's membrane is disrupted by degeneration and distortion of fibers by accumulations of abnormal material (Gregor, 1977); 2) that CNV produces breaks in Bruch's membrane (Heriot, 1984); 3) that progressive scleral rigidity impedes venous outflow resulting in vascular stagnation in the choroid and accumulation of sub-RPE debris (drusen) leading to CNV (Friedman, 1989; Friedman, 1995); and 4) that the diffusely thickened inner aspect of Bruch's membrane creates a diffusion barrier that interferes with normal function of the retinal pigment epithelium which may cause the release of angiogenic agents (Jacobson, 1995).

### 1.4. PUBLIC HEALTH SIGNIFICANCE

Age related macular degeneration is the leading cause of blindness among the elderly in the United States and other Western countries (Tielsch, 1994; Sommer, 1991; Leibowitz, 1980; Klein, 1992; Sorsby, 1966). The great majority of severe visual loss due to AMD is attributable to CNV (Ferris, 1983; Sommer, 1991). Approximately 230,000 people in the United States are believed to be legally blind due to AMD (Tielsch, 1994). The prevalence of the late forms of AMD in whites increases sharply from 0.1% in those aged 43 to 54 years to 1.4% in those aged 65 to 74 years and to 7.1% in those older than 75 years (Klein, 1992). More than 1.2 million people currently have one or both eyes affected by the late stage of AMD (Tielsch, 1994). The incidence of CNV in either the first or second eye has been estimated to be approximately 200,000 per year (Hawkins, unpublished). These numbers are expected to increase as the proportion of the American population over the age of 65 years increases. Current projections

by the US Census Bureau have the US population aged 65 years and older increasing 63% from 32,800,000 in 1993 to 53,350,000 by 2020. (USA Today, 1996).

### **1.5. TREATMENT OF CNV**

The only proven treatments for established CNV are focal laser photocoagulation (MPS, 1991; MPS, 1993; MPS, 1994) and PDT with verteporfin (Treatment of Age-related Macular Degeneration with Photodynamic Therapy Study Group, 1999). Although laser photocoagulation treatment of eligible lesions results in better visual function than no treatment of those lesions, the benefit is modest. More than half of treated eyes develop persistent or recurrent CNV within 5 years. The average visual acuity of treated patients is 20/250 -- 20/320. Furthermore, laser photocoagulation is beneficial for only those eyes with well demarcated lesions of relatively small size. Such lesions account for less than 20% of all lesions (Bressler, 1987; Freund, 1993). PDT is beneficial for patients with predominately classic CNV, especially in the absence of occult CNV lesions. For these patients, PDT can reduce the risk of moderate vision loss for at least one year (Bressler & Bressler, 2000). Thus, more than half of all lesions are not amenable for any proven treatment for established CNV. In addition, most patients need to be treated with PDT every 3 months for an indefinite period of time. Some patients may object to the frequent angiography and treatment.

Alternative treatments for established CNV are under investigation. These treatments are aimed at preventing further deterioration in vision from the already decreased level at presentation. Studies of submacular surgery to remove the CNV (Bressler, 1997), and radiation therapy to contain the lesion without destroying overlying retina (Chakravarthy, 1993; Finger, 1996), and thalidomide to slow the rate of abnormal blood vessel growth (D'Amato, 1994) have been initiated. Even if these treatments prove to be beneficial compared to observation or to laser treatment, the vision in the affected eye still will be substantially impaired. While patients may benefit from them, these treatments will not have a major public health impact on the rate of blindness from AMD.

### **1.6. RISK FACTORS FOR AMD**

The high prevalence and impact of AMD have led to a number of investigations for risk factors (Maltzman, 1979; Delaney, 1982; Hyman, 1983; Goldberg, 1988; Vinding, 1992; Eye Disease Case-Control Study Group, 1992, 1993; Sandberg, 1994; Seddon, 1994; Hirvela, 1996). Risk factors for non-neovascular AMD appear to differ from risk factors for neovascular AMD in some respects. The most consistently identified factors for neovascular AMD include: family history, smoking, cardiovascular disease, hyperopia, white race, light eye color, and low dietary intake of antioxidants.

Several studies have investigated specific fundus features believed to identify eyes at the highest risk of developing CNV. The contralateral, or fellow, eye of an eye with CNV has been documented to have a very high risk of developing CNV. Annualized rates (cumulative incidence divided by follow-up time) vary from a low of 4% (Roy, 1990) to a high of 18% (Chandra, 1974). Larger studies have provided annualized rates of 8% (Gass, 1973), 5% (Strahlman, 1983), 6% (Bressler [MPS], 1993), 12% (Gregor, 1988), and 8% (Baun, 1993). One

source of variation in these studies may have been the distribution of large drusen in the study groups. In the first MPS study of fellow eyes reported by Bressler and coworkers, the annualized rate varied from 2% for eyes with no large drusen or focal areas of macular hyperpigmentation, to 6% for eyes with one or the other of these features, to nearly 12% for eyes with both features. A more recent report from the MPS on an independent group of 670 fellow eyes confirmed the increase in risk associated with large drusen and focal hyperpigmentation and also identified number of drusen and systemic hypertension as independent risk factors (MPS, 1997). The subgroup of eyes with none of these 4 factors had an annualized risk of less than 2% while the subgroup with all four factors had an annualized rate of 17%. In the study by Strahlman and coworkers, the annualized rate for the subgroup of eyes with confluent soft drusen was 18%.

Patients with bilateral large drusen also have been shown to be at excess risk of developing CNV. Gass in 1973 reported an annual incidence rate for CNV in one or both eyes of approximately 4% per year; however, the rate in this early study was not specific to any particular type of drusen. Smiddy, Fine, and Hillis reported a rate of 2% per year (Smiddy, 1984). Recently, Holz (1994) reported an incidence rate of approximately 4% per year for exudative lesions; however, this rate increased to 6% when only those 65 years of age and older were considered and to 9% when only those aged 65 and older with large drusen were considered. Central focal hyperpigmentation was also associated with a high incidence rate.

Fellow eyes of patients with unilateral neovascular AMD show deficiencies on electrophysiological testing (Eisner, 1991; Sandberg, 1993; 1995). The severity of deficiency appears to be related to the risk of developing advanced AMD (Sunness, 1989; Eisner, 1992).

## **1.7. EFFORTS TO PREVENT CNV**

Given the tremendous impact of CNV in the expanding elderly population, there is an obvious need for prevention of the ingrowth of new vessels before there is severe loss of visual function. To date, there are no proven treatments for the prevention of CNV. There are, however, a number of preventive strategies now under consideration.

The National Eye Institute is sponsoring the Age-Related Eye Disease Study (AREDS). AREDS is a multicenter, clinical trial to evaluate the role of supplementation with a combination of antioxidant vitamins and the role of zinc supplementation in the development of age-related macular degeneration and cataract. As noted above, high levels of antioxidant intake and of plasma concentrations have appeared to be protective in observational epidemiological studies (Seddon, 1994; Eye Disease Case-Control Study Group, 1993; Sperduto, 1990; Goldberg, 1988; West, 1994). A clinical trial on a select population in Utah has provided support for the role of zinc supplementation in protection of people from advancing macular degeneration (Newsome, 1988). However, a recent 2-year, double masked, randomized clinical trial of 112 patients with unilateral disease failed to show a protective effect; in fact, approximately 20% of the zinc treated eyes versus 11% of the placebo treated eyes developed CNV (Stur, 1996). In AREDS, four categories of patients with AMD, varying in severity from no drusen or only a relatively small number of hard drusen bilaterally to

advanced AMD in one eye, have been enrolled. One thousand or more patients have been recruited into each of the four categories.

Follow-up of patients in AREDS is expected to continue until the year 2000. Even if either antioxidant or zinc supplementation prove to be effective in reducing the risk of advanced AMD, investigation of preventive laser treatment will still be important. These supplements are very unlikely to "cure" AMD. The proposed biologic actions of both the antioxidants and zinc are in the prevention of damage at the level of the RPE and should be independent of the proposed action of the laser treatment. In other words, any effects of antioxidant and zinc supplementation and laser treatment should be additive.

## **1.8. EARLY INVESTIGATIONS OF PHOTOCOAGULATION FOR EYES WITH DRUSEN**

During the early 1970's, Gass was among the first to propose prophylactic laser treatment for eyes at high risk of CNV (Gass, 1971). He had observed a decrease in drusen in eyes treated with focal photocoagulation of established CNV. Cleasby treated one eye of 25 patients with bilateral drusen and the fellow eye of 29 patients with neovascular AMD with 200 to 300 burns in a circular pattern around the fovea (Cleasby, 1979). Among fellow eyes, the annualized rate of CNV was 4.4% over an average of 28 months. No CNV developed in patients with bilateral drusen. Cleasby reported no immediate complications. Wetzig treated one or both eyes of patients with soft drusen and recent *progressive* loss in visual acuity or metamorphosis (Wetzig, 1988). Eyes were treated with 50 to 75 burns around the fovea in a scatter pattern without specific direction to drusen. Decrease in drusen and stabilization of vision were observed in 52% of patients (average follow-up of 3.7 years). Wetzig reported no complications associated with the treatment.

## **1.9. CHANGES IN DRUSEN IN EYES WITH NO TREATMENT**

Interpretation of reports of decreases in drusen must include consideration of the fact that drusen can disappear without any intervention. Gass, Sarks, and others have described the natural progression of soft drusen as confluence leading to a small retinal pigment epithelial detachment, then fading to leave behind pigment mottling and/or atrophy in some cases (Gass, 1973; Sarks, 1980; Sarks, 1994). Bressler reported that, within a 5 year period, all large drusen disappeared in 34% of eyes with very early changes consisting of only one or a few large drusen (Bressler, 1995). Within fellow eyes of patients enrolled in the Macular Photocoagulation Study because of unilateral CNV, areas of large drusen disappeared with no new large drusen in another area in 13% of eyes within a two year period (Javornik, 1992). Large drusen disappeared from one or more areas and new large drusen appeared in other areas of the macula in an additional 13% of those eyes.

## **1.10. MECHANISM FOR PREVENTION OF ADVANCED AMD BY LOW INTENSITY LASER PHOTOCOAGULATION**

The pathogenesis of CNV from AMD is not known. As discussed in section 2.2, there are some theories on the development of new vessels, but none have been proven. Therefore, the

exact mechanism by which any intervention, including supplementation with antioxidant vitamins and zinc, might prevent the development of CNV is speculative.

Duvall and Tso have studied the histopathology of the eyes of an adult rhesus monkey with naturally occurring hard drusen that were treated with mild grayish laser burns (Duvall, 1985). After treatment, they observed the breakdown of drusen material as well as infiltration and clustering of macrophages within the subretinal space. Cell processes of the macrophages were noted to have phagosomes containing fragments of necrotic retinal pigment epithelial cells, photoreceptor cells, and drusen material. In addition, another phagocytic cell type, apparently derived from pericytes of the choriocapillaris, was noted to be removing drusenoid material after laser photocoagulation.

Duvall and Tso postulated that the mild tissue damage around drusen treated with laser photocoagulation stimulates a reactive process that removes drusen. Clinical observations have documented repeatedly that there is an effect of photocoagulation remote from the site of treatment. The debris removing activities of the macrophages may therefore extend to surrounding areas of diffusely thickened Bruch's membrane. Consistent with this theory, Green has noted that basal linear deposits outside the area of direct treatment are reduced after laser photocoagulation of CNV (personal communication). Reduction of the disruption of Bruch's membrane may be achieved by removing drusen and by reducing basal linear deposit. The return to a more normal morphology may increase the capability of Bruch's membrane to act as a physical barrier to choroidal vessel ingrowth.

Other proposed mechanisms for the effect of laser photocoagulation on drusen and the development of CNV include the following:

- Laser photocoagulation may destroy deteriorated RPE cells that would otherwise contribute to drusen formation (Figueroa, 1994).
- Laser photocoagulation may increase the egress of drusen material from beneath the RPE and thickened Bruch's membrane and thereby cause drusen to disappear (Sigelman, 1991).
- Laser photocoagulation scars may create a barrier preventing the centripetal flow of drusen from the retinal periphery (Sigelman, 1991).
- Mild laser photocoagulation causes a piling up of RPE cells that stimulate the release of an inhibitory factor for neovascularization (Patz, 1988; Glaser, 1985; Yoshimura, 1995; Matsumoto, 1994).

## **1.11. STUDIES OF LASER TREATMENT WITHOUT CONTROLS**

### **1.11.1. Foveal Drusen Resorption After Perifoveal Laser Treatment**

In 1991, Sigelman reported treatment of an eye that had large, confluent drusen throughout the macula including the fovea (Sigelman, 1991). The eye was treated with 56 spots of 200 microns to produce a gray-white burn in large drusen in the temporal macula and in a nearly horseshoe pattern peripheral to the drusen to continue the grid of photocoagulation where

there were no drusen. All burns were >500 microns from the foveal center. Six months later, 76 additional burns were applied outside the region of the previous treatment. Six months after the first treatment, treated drusen were barely apparent on biomicroscopy. The untreated foveal and perifoveal drusen were diminished in mass. Visual acuity had improved by one line to 20/30. Six months after the second treatment, there was further reduction in drusen, including the complete disappearance of the foveal drusen. Visual acuity had improved to 20/20. The magnitude of the reduction in drusen and the close timing of the reduction to treatment provide evidence that application of laser burns in one part of the posterior pole can be responsible for the reduction in the extent of drusen in another part of the posterior pole, including the fovea. Resolution of subfoveal drusen also was accompanied by improvement in visual acuity.

#### **1.11.2. Pilot Study in Madrid, Spain**

Figueroa and coworkers in Madrid, Spain published results of a prospective pilot study of 20 patients with confluent soft drusen involving the fovea (Figueroa, 1994). Treatment involved application of a 100 micron spot on each druse in the temporal macula. The intensity was set to produce a light, gray-white lesion. No treatment was applied within 500 microns of the center of the fovea. If all the drusen were within the avascular zone, two crescent-shaped vertical rows of laser spots were applied to the temporal macula, at least 500 microns from the foveal center. Between 18 and 72 spots were applied. Treated temporal drusen disappeared first (mean time, 2 months), followed by subfoveal drusen, and finally nasal drusen. Follow-up ranged from 7 to 25 months with a mean of 18 months. Visual acuity improved by one line in 5 (25%) patients and by 2 lines in 1 (5%) patient. One eye (5%) developed CNV in a location *not involved in the laser treatment*. Ten degree visual fields were tested by automated perimetry at baseline and during follow-up. Only the patient who had CNV had a scotoma. No enlargement of the laser scars was noted during follow-up.

#### **1.11.3. Pilot Study in London, England**

Bird and coworkers at Moorfields Eye Hospital treated one eye of each of 12 patients with 12 laser burns (Guymer, 1997). Five patients received an additional 5 to 16 burns between 3 and 14 months because drusen remained unchanged. One patient (8%) developed CNV away from the laser sites at 8 months. By one year, nine of the remaining 11 had a substantial reduction in drusen. Two patients developed atrophy at the site of a laser burn that did not enlarge over time.

#### **1.11.4. Clinical Trials of Laser Treatment in Eyes with Large Drusen**

Dr. Shirley Sarks and co-workers in Australia have initiated a randomized clinical trial of laser photocoagulation for patients with high risk drusen. Mr. Alan Bird at Moorfields has initiated a similar clinical trial. Dr. Figueroa has initiated a randomized clinical trial in Spain. Drs. Peep Algvere and Goran Olivestedt of Stockholm have been conducting a randomized clinical trial in 32 bilateral drusen patients. Drs. Susan and Neil Bressler and Lawrence Singerman in the US have enrolled approximately 60 fellow eyes in a randomized trial initiated in 1994. Most of these groups are using either a temporal horseshoe shaped grid or a doughnut shaped grid around the fovea and low intensity burns. Drs. Thomas Friberg and



Joseph Olk in the US have led an industry sponsored (IRIS Medical) pilot trial of diode laser treatment involving a second randomization to either threshold or subthreshold burns. No results have been published from any of these studies. During the 1997 ARVO meeting and subspecialty meetings, the IRIS group reported less CNV in the subthreshold burn group than in the threshold burn group in their study.

Dr. Hunter Little published the results of a clinical trial of 27 patients with bilateral drusen in which one eye was selected for treatment on the basis of birth month (Little, 1997). Focal treatment was applied directly to drusen; 23 to 516 (mean 132) burns were applied with a desired intensity of “slightly visible lightening”. Follow-up ranged from 1 to 6 years (mean 3.2). Additional photocoagulation was applied if drusen persisted. Treated eyes had mean visual acuity 1.2 lines better than their untreated fellow eyes. Twelve patients had better vision in their treated eye, 2 patients had better vision in their untreated eye, and 13 patients had equal vision in each eye ( $p=.006$ ). CNV developed in two patients in both eyes and in 2 patients in the untreated eye only.

A second Swedish group led by Drs. I. Christina Frennesson and Sven Nilsson has conducted a clinical trial in a group of 38 eyes composed of one eye of 22 patients with bilateral drusen and 16 fellow eyes in which 50% of the eyes were randomly assigned to laser treatment and 50% to observation (Frennesson, 1995; Frennesson, ARVO 1997). Fifty-one to 154 (mean 100) grayish spots were applied in a horseshoe pattern and directly to drusen. Twelve-month results showed reduction of the drusen area by 50% on average, by both fluorescein angiography and color stereo photography. By 36 months, untreated eyes had significantly worse vision from baseline ( $p=.01$ ) while treated eyes remained stable. Five treated eyes (four of bilateral drusen patients and one fellow eye) developed CNV while none of the untreated eyes did ( $p=0.047$ ).

## 1.12. PILOT STUDY FOR CAPT

At the end of 1994, the planning group for CAPT initiated a pilot study, the Choroidal Neovascularization Prevention Trial (CNVPT). Patients were first recruited only at the Scheie Eye Institute but eventually 15 other clinical centers enrolled patients. The CNVPT had two distinct substudies: the Bilateral Drusen Study for patients with two eyes with large drusen and no exudative AMD and the Fellow Eye Study for patients who had one eye with exudative AMD and the other eye with large drusen. The major objectives of the pilot study were to:

- Establish the effects of various laser treatment protocols in reducing the area of drusen;
- Confirm the short term safety of laser treatment;
- Test and refine data collection and other procedures;
- Provide a basis for establishing realistic recruitment goals for a definitive trial.

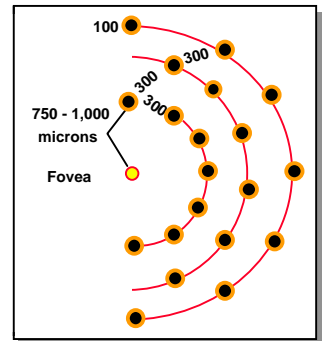
A planning grant for CAPT was applied for in February 1995 and was awarded in February 1996. In late December 1996, the Data and Safety Monitoring Committee recommended suspension of recruitment and laser treatment in the CNVPT and dissemination of the data to the ophthalmologic community. The recommendations were based on the observation of a higher proportion of predominantly fellow eyes in the treated group developing CNV in the first year after enrollment. The results were reported verbally at meetings of retinal specialists, at ARVO, and at the AAO during 1997. A manuscript based on the data available through March 28, 1997 was published in January 1998 (CNVPT Research

Group, 1998a). The following subsections describe how the CNVPT objectives were met and the CNVPT results.

### 1.12.1. Effects of laser treatment in reducing drusen in the CNVPT

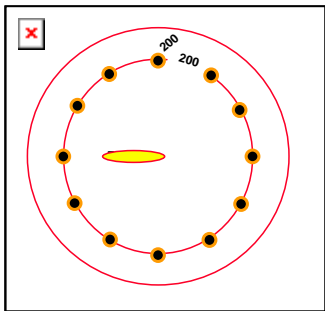
The first laser treatment protocol (Laser-20 protocol) evaluated in the CNVPT involved placement of 20, 100 micron burns in a pattern of 3 rows, situated from 12 o'clock to 6 o'clock (180 degrees), around the temporal perimeter of the foveal center with the distance of the first row of 7 burns at least 750 microns from the foveal center. The desired intensity was to produce a light gray-white lesion. Direct application of laser burns over drusen was to be avoided. Eyes without a 50% reduction in the area of drusen at 6 months had a second treatment on the nasal side of the fovea using the same 180 degree pattern.

Initial Laser-20 treatment

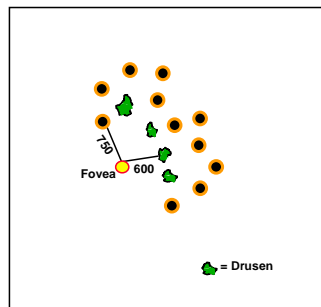


As of June 30, 1996, among the 64 eyes that had been treated and evaluated at 6 months after study enrollment, only 16 (25%) had reached a 50% reduction in the area of drusen. Thus, retreatment was necessary in 75% of eyes assigned to treatment. Based on these findings, the CNVPT research group decided to implement a new treatment protocol (Laser-24 protocol) that they believed would provide more uniform and rapid reduction of drusen throughout the macula. Under the new protocol, initial treatment would consist of 24 100 micron burns, in 2 rows of 12 in a circular pattern (360 degrees) centered on the fovea and surrounding the area of macular drusen. At 6 months, if 10 or more large drusen were still present, the treatment would be repeated, again surrounding the area of remaining drusen. At 12 months treatment would be repeated to surround the remaining drusen, not necessarily centered on the fovea. For each treatment session, burns were not to be closer than 750 microns from the fovea, over existing or resolved drusen, or over old treatment burns. By the time recruitment and treatment were suspended, 32 (15%) of the 215 eyes assigned to treatment (23 in the Bilateral Drusen Study and 9 in the Fellow Eye Study) had been treated under Laser-24. No eyes had yet been retreated at 6 months under Laser-24.

Initial & Retreatment Laser-24



Retreatment at 12 months



**Note:** No treatment can be applied between fovea and remaining drusen because treatment would be <750 microns from fovea center

\* The location of old burns can be determined from indirect (retro) illumination, reference to a photograph taken after previous treatment, or reference to an angiogram taken after previous treatment, if available.

There was increased resolution of drusen in treated eyes over follow-up. Reduction in the area of treatment was more extensive on the temporal side, the side treated at baseline under Laser 20, at 3 and 6 months. By 12 months, after approximately 75% of the eyes had been retreated on the nasal side, the area of drusen was less on the temporal side of the fovea in

approximately 90% of eyes. There was also a reduction on the nasal side in 90% of the eyes. The proportion of eyes with a 50% reduction in the total area of drusen increased over time; however, a substantial proportion of eyes had not had such dramatic reduction by 12 months. Only one untreated eye had a 50% reduction by 6 months.

These data clearly demonstrated that laser treatment, for the most part carried out under Laser 20, was responsible for:

- Reduction of drusen even when drusen were not treated directly;
- Reduction of drusen in the area of treatment in the majority of eyes;
- Reduction of drusen in the area not treated in the majority of eyes (reduction at 3 and 6 months nasal to the fovea);
- More reduction in the area of treatment than in the area not treated;
- Dramatic (50%) reduction in drusen within 6 months only 25-30% of the time.

### 1.12.2. Short Term Safety of Laser Treatment

There were no immediate complications (hemorrhage, breaks in Bruch's membrane, etc.) in eyes at the times of treatment or retreatment among the 215 eyes assigned to laser treatment. Some patients reported "seeing" the spots immediately after treatment. When questioned about changes in their vision since the initial visit, approximately 4% of treated patients reported at their 3-month visit that they could see the spots or flashes of light around the spots. The perception of these spots decreased with time. Ronald Schuchard, Ph.D., working in collaboration with Felix Sabates, M.D., examined their 19 CNVPT patients at each visit with a scanning laser ophthalmoscope. With follow-up, the size of the relative scotoma coincided with the laser burn and there was no increase in size over time through October 1997. Scotomas of this size are not detectable with an automated perimeter, such as the Humphrey Visual Field Analyzer.

There was an unexpected, higher rate of CNV development in treated eyes in the Fellow Eye Study. The CNVPT Data and Safety Monitoring Committee deemed the findings of sufficient concern to patient safety that they recommended: 1) the suspension of all patient enrollment and treatment; and 2) further follow-up of all patients to assess the duration of increased risk of CNV in treated eyes and the long term effects of CNV on visual function. By March 28, 1997, ten of 59 treated eyes and two of 61 untreated fellow eyes had developed CNV ( $p=.02$ ). Only six of the 312 eyes of patients with bilateral drusen had developed CNV, four in the treated group and two in the untreated group ( $p=.69$ ). The CNV that developed in treated eyes was predominantly occult CNV in the general area of the laser treatment (CNVPT Research Group, 1998b). Despite the higher rate of CNV in treated fellow eyes, absolute visual acuity and loss in visual acuity actually favored treated eyes at 12 and 18 months. Only two of the eyes that developed CNV had been followed for a year or more after developing CNV. There were no consistent trends in visual acuity in the Bilateral Drusen Study.

In the absence of other data from controlled trials of laser treatment for fellow eyes, the CNVPT short term results convinced the CNVPT Research Group not to pursue additional investigation of laser treatment in fellow eyes at the time of the initiation of CAPT. The low event rates in the CNVPT Bilateral Drusen Study did not raise concern over the short term safety of laser treatment in eyes of patients with bilateral drusen.

The above results have led to speculation on the possible effects of low intensity laser burns. Laser treatment may initiate two processes: 1) Recruitment of macrophages and other phagocytic cell types to remove drusen and debris from surrounding areas of Bruch's membrane in response to laser induced inflammation; and 2) Disruption of the usual biochemical equilibrium between stimuli and inhibitors of angiogenesis. The disruption may be mediated by either the activity of stimulated RPE cells or the macrophages. Either cell could elaborate FGF, VEGF, or other growth factors that might be responsible for temporarily stimulating local vascular endothelial cells. Further discussion of the interpretation of the CNVPT results and their impact on the rationale for CAPT is found in section 1.14.

### **1.12.3. Test and Refine Data Collection and Other Procedures in the CNVPT for Use in CAPT**

Approximately 30 forms for data collection and transmission were developed for the CNVPT. The forms worked well in that the clinic coordinators and ophthalmologists had relatively few questions about the correct way to complete the forms. However, a few poorly constructed questions were identified and modified. Forms were also revised to reflect changes in the protocol. Conversion of the existing forms enabled relatively fast generation of forms for CAPT. The last major component to the data management system, the post data entry editing system, was put into action in Summer 1997.

Performance of the CNVPT clinical centers was good. As of the time of the submission of the grant application for CAPT, only 4% of the expected 697 visits had been missed. Nineteen (4%) of the 432 eyes were declared ineligible. Seven (1.6%) of the eyes had angiographic evidence of early CNV at baseline detected by the Reading Center. The remaining 12 eyes were ineligible on the basis of visual acuity (two eyes: 1 and 2 letters too low) and 10 for the presence of geographic atrophy, pigment epithelial detachment, or other ocular disease beyond the extent allowable by the final CNVPT protocol. Also, two early patients refused treatment after randomization. Except for the enrollment of eyes with early angiographic signs of CNV that occurred throughout the enrollment period, most of these problems occurred early in the pilot study as some of the eligibility criteria were being defined and some of the clinic coordinators were new to their positions. Ineligible patients were subject to the same follow-up as eligible patients.

### **1.12.4. Provide a Basis for Establishing Realistic Recruitment Goals for CAPT**

Little emphasis was placed on volume of patient recruitment since the CNVPT clinical centers were not provided with any funding and the costs of laser treatment were to be absorbed by the clinical center. Emphasis was put on appropriate patient selection and complete follow-up. In general, no efforts were made to secure patients from referral sources.

Despite these circumstances, 15 clinical centers completed CNVPT clinic certification procedures and enrolled an average of 1.3 patients per month (median=1.2, range .2 to 2.8). Approximately 55% of these patients were enrolled in the Bilateral Drusen Study.

#### **1.12.5. Other Refinements to the Objectives of CAPT Based on CNVPT Experience**

As evidenced by the name “Choroidal Neovascularization Prevention Trial”, the emphasis in the CNVPT was on the development of CNV. While the overwhelming majority of vision loss in AMD is from CNV (MPS [Fellow Eye], 1993), pigment epithelial detachments (PEDs) may also cause loss of vision, regardless of whether new vessels are present or later develop. Although none have developed in enrolled eyes during the course of the CNVPT, a serous PED would have to be viewed as a failure of the laser treatment in protecting the eye. Also, investigators wanted to exclude eyes in which geographic atrophy had already progressed to involving areas within 500 microns of the foveal center thereby posing a serious threat to central vision. However, if laser treatment is successful in reducing the thickness of Bruch’s membrane (see section 1.13 below) and reducing the area of drusen, known precursors of geographic atrophy (Sarks, 1994), then the incidence of new geographic atrophy might also be reduced. Alternatively, laser treatment might accelerate the development of geographic atrophy. However, reports by other investigators of geographic atrophy have shown atrophy confined to the treatment area without spread into the fovea.

Based on the above considerations, loss of visual acuity is the most appropriate outcome to measure the effectiveness of laser treatment because it incorporates the potential beneficial effects of the treatment through reducing the incidence of all advanced forms of AMD and the possibly harmful effects of stimulating new vessels and accelerating geographic atrophy.

#### **1.13. EVALUATION OF THE IMPACT OF INTERVENTIONS TO PREVENT THE DEVELOPMENT OF CNV AND THEIR ECONOMIC IMPACT**

During the planning phase of CAPT, Ms. Diana Lanchoney, a fourth year Penn medical student with a background in economics and finance, developed a model of the incidence of CNV and subsequent bilateral legal blindness that incorporated mortality, current laser treatment and preventive interventions of varying effectiveness. She then applied that model to a prevalence cohort of patients with bilateral high risk drusen. Preventive treatment of both eyes of the cohort at the outset, as well as preventive treatment of the fellow eye after one eye had developed CNV, were investigated (Lanchoney, 1998). Using the prevalence rates of bilateral soft drusen from the Beaver Dam Study applied to the age-sex structure of whites in the United States with published rates of CNV incidence, the model showed that 10 years after entry into the cohort, 12.7% of the group would have developed CNV in one or both eyes. The rate would be reduced by 28% to 9.1% if an intervention that was 30% effective in preventing CNV were applied to both eyes at entry into the cohort. Legal blindness at 10 years would be 2.1% with no treatment of any kind, 1.8% with treatment of CNV amenable to laser treatment, and 0.9% if a 30% effective preventive intervention were applied to both eyes at onset. This is a 50% reduction from the rate with current treatment of CNV. Thus, a preventive laser treatment of only 30% effectiveness would have a tremendous impact on the number of

patients affected with CNV and the number of patients with severe, bilateral visual impairment (20/200 or less).

#### **1.14. SUMMARY OF THE RATIONALE FOR CAPT WITH BILATERAL DRUSEN EYES ONLY**

The preceding sections have provided the background and potential impact of laser photocoagulation as a preventive treatment for eyes with large drusen. We believe that the rationale for a definitive trial is compelling because:

- Identification of a preventive treatment, even one that was only modestly effective, would have a tremendous public health impact in the US and many western countries.
- The presence of large drusen is a strong risk factor for the late complications of AMD that are responsible for the most severe loss of vision.
- Although the biologic mechanism for the effects of laser treatment are not known, there is no doubt that the treatment causes resolution of drusen both in the area of direct treatment and in areas remote from the treatment.
- Eyes of patients with bilateral large drusen and fellow eyes of patients with unilateral neovascular AMD may appear to be similar on the basis of ophthalmoscopic and angiographic features yet their risk of developing exudative disease is very different (three-fold difference). Patients who have already developed CNV in one eye must have unknown additional conditions that increase the risk of formation of new vessels in the fellow eye.
- It is reasonable to believe that the overall response to low intensity laser burns could differ between these two groups of patients. For example, laser treatment may temporarily disturb the usual equilibrium between stimuli and inhibitors of angiogenesis. In the fellow eye, this altered biochemical environment may promote the development and/or progression of the earliest stages of new vessels resulting in a short-term increase in CNV after treatment. Conversely, in lower risk bilateral drusen eyes, the disturbance may have a dampened short term effect that is insignificant compared to the decrease in long term risk that accompanies the resolution of drusen.
- Although many groups in this country and others are conducting small pilot trials of preventive laser treatment, predominantly in eyes of patients with bilateral drusen, no other group has reported adverse effects of laser treatment. The two small pilot clinical trials that have released results have longer follow-up than the CNVPT and have shown beneficial effects on both the development of the late complications of AMD and on vision.

The promise shown by low intensity laser treatment and the high incidence and severity of the late complications of AMD demand a well conducted clinical trial in patients with bilateral drusen. Until there is additional information about the long-term effects of laser treatment on the incidence of CNV and the impact of the CNV on vision, it is prudent to postpone any decision about further investigation in fellow eyes.



## CHAPTER 2

### RESEARCH DESIGN SUMMARY

#### 2.1. DESIGN SUMMARY TABLE

**Table 1. Design Summary of the CAPT**

Feature	CAPT Criteria
Objective	Evaluate laser treatment in preventing vision loss from AMD
Major Eligibility Criteria	$\geq 10$ large drusen in each eye Visual acuity $\geq 20/40$ in each eye
Randomization Unit	Eye within person
Treatments	Laser treatment – Initial: 60 burns, grid pattern - Retreatment at 12 m: 30 burns, focal treatment Dependent on resolution of drusen
	Observation
Outcome Measures	
Primary	Change in visual acuity
Secondary	Incidence of CNV, PED, GA Contrast threshold Reading (critical print size)
Descriptive Measures	Quality of life (NEI-VFQ-25)
Sample size	1000 people (2000 eyes)
Length of Follow-up	5 years

## CHAPTER 3

### ORGANIZATIONAL STRUCTURE OF THE STUDY GROUP

#### 3.1. INTRODUCTION

The Study organization consists of an Operations Committee, Executive Committee, the Investigative Group, a Data and Safety Monitoring Committee, a Clinic Monitoring Committee, and other committees as required. The functional units in the Complications of Age-related Macular Degeneration Prevention Trial (CAPT) are the Clinical Centers, the Fundus Photograph Reading Center, and the Coordinating Center.

#### 3.2. OPERATIONS COMMITTEE

The Operations Committee has responsibility for handling study issues in a timely manner between meetings of the Executive Committee. Issues regarding overall study progress, areas of particular concern with respect to performance of any of the CAPT centers, and publicity are typically addressed by this committee. In general, changes to the protocol will not be made without convening the Executive Committee.

##### 3.2.1. Membership

The members of the Operations Committee are the CAPT Chair, the Director of the Coordinating Center, the Principal Investigator of the Photograph Reading Center, the Director of the Reading Center, Project Director of the Coordinating Center and a representative from the National Eye Institute. Other members of the Investigative Group will be invited to participate on an as needed basis.

##### 3.2.2. Meetings

Meetings of the full committee will be scheduled on a monthly basis, but the schedule will be changed to address emergency situations as needed. Additional meetings of the CAPT Chair, the Director of the Coordinating Center, and Principal Investigator of the Reading Center will occur as needed, with more frequent meetings likely during the start-up phase of CAPT.

#### 3.3. EXECUTIVE COMMITTEE

The Executive Committee has overall responsibility for directing the activities of the Study. The Executive Committee will be responsible for the major scientific leadership of the CAPT; providing approval for all ancillary studies, abstracts, presentations, and papers; making changes in the CAPT protocol, and advising on matters of publicity and recruitment. The committee meets twice a year - once in conjunction with the Investigative Group and once independently.

### 3.3.1. Membership

The permanent members of the Executive Committee are the Study Chair (who also serves as Chair of the Executive Committee), the Director of the Coordinating Center, the Director of the Reading Center, the Principal Investigator of the Reading Center, the Project Director of the Coordinating Center, a representative designated by the National Eye Institute, and two ophthalmologists. In addition, three CAPT-certified ophthalmologists are designated to serve for one-year terms. A Clinic Coordinator will also be selected to serve on the committee for a two-year term. Other study personnel or individuals may be invited to attend one or more Executive Committee meetings at the discretion of the Committee and/or Study Chair.

The rotation of ophthalmologists onto the Executive Committee is in clinic order. In general, rotating membership is the prerogative of the Principal Investigator, but another CAPT-certified ophthalmologist from the same clinic may be designated by the Principal Investigator to serve in his/her place. Only clinics actively engaged in all aspects of patient recruitment, treatment, and follow-up are eligible for representation on the Executive Committee. Ophthalmologists serve for one year, beginning at the first of the month of their first Executive Committee meeting during that period. The clinic coordinator representative on the committee will serve a two-year term, beginning at the first of the month of his/her first Executive Committee meeting during that period.

### 3.3.2. Functions

Some specific functions of the Executive Committee are:

- To approve such changes or modifications in the specifications of treatment techniques as may be necessary or desirable;
- To give approval of major changes in the *CAPT Manual of Procedures*;
- Through subcommittees and individuals, to advise and assist the Coordinating Center on operational matters;
- To resolve operating problems brought to the Executive Committee by investigators, the Coordinating Center, and the Reading Center;
- To monitor the performance of all participating centers. In this regard, the committee utilizes information provided by the Coordinating Center to evaluate the quality of data collected by the individual centers and their adherence to protocol. As needed, the Executive Committee schedules problem-solving visits to appropriate participants. Any clinic that is behind schedule in meeting its recruitment goals, whose fundus and/or fluorescein photographs are consistently judged unsuitable by the Reading Center, whose treatments are consistently considered inadequate by the Reading Center, or that fails to adhere to protocol according to report of the Clinic Monitoring Committee is reviewed by the Executive Committee as to whether that clinic should continue to participate in the Study.
- To ensure enforcement of the editorial policy specified in Chapter 4.4.

- To approve ancillary studies and to monitor the progress of those approved.
- To appoint subcommittees as necessary.

### **3.4. INVESTIGATIVE GROUP**

The Investigative Group represents all of the operational units participating in the Study and is responsible for maintaining a protocol that is specific, practical, and well-understood by all participants.

#### **3.4.1. Membership**

All certified members of the CAPT study group are members of the Investigative Group. This includes the Principal Investigator, Participating Ophthalmologists, Clinic Coordinator, Visual Function Examiners, and Photographers from each Clinical Center, staff members of the Coordinating Center and Reading Center, and the representative of the National Eye.

#### **3.4.2. Meetings**

The Investigative Group meets once each year to review the progress of the study and to solve problems that have arisen in carrying out the protocol. In general, the Clinic Coordinator and Principal Investigator from each clinical center are required to attend; other members of the Investigative Group may attend. Separate sessions for Clinic Coordinators are usually part of the Investigative Group meetings. Separate meetings of other clinic personnel are scheduled as necessary. Individuals not associated with the CAPT may be invited by the Study Chair, but only if exceptional circumstances arise requiring their attendance for the benefit of the Study.

### **3.5. DATA AND SAFETY MONITORING COMMITTEE**

The responsibility for reviewing the ethical conduct of the Study and for monitoring the data for evidence of adverse or beneficial treatment effects is assigned to the Data and Safety Monitoring Committee (DSMC). Results are not available to the participating ophthalmologists who are treating patients (except for the Study Chair) until the Data and Safety Monitoring Committee decides to release the information.

Results of all data analyses involving comparisons of treated and untreated eyes are first presented to the Data and Safety Monitoring Committee unless this committee has given other instructions.

#### **3.5.1. Membership**

The CAPT Data and Safety Monitoring Committee consists of three ophthalmologists, two biostatistician/epidemiologists, and a patient advocate as voting members (total 6). The Director, Project Director, and Systems Analyst of the Coordinating Center, Study Chair, and NEI representative serve as ex officio members. Executive sessions of the voting members only may be held as deemed necessary by the chair of the Data and Safety Monitoring Committee. The Chair of the Data and Safety Monitoring Committee may appoint additional members as appropriate.

### 3.5.2. Functions

The Data and Safety Monitoring Committee reviews the initial design of CAPT, including the recruitment methods and the protocol recommendations pertaining to informed consent. The Committee decides what role, if any, the CNVPT pilot study data should have in the evaluation of the CAPT data. The Committee is advisory to the National Eye Institute.

The Data and Safety Monitoring Committee periodically reviews the Study results (at least once each year) and evaluates the laser treatment for beneficial and adverse effects. The Data Monitoring Reports, distributed by the Coordinating Center, are reviewed *only* by the Data and Safety Monitoring Committee until such time as the data indicate that a change of protocol is required. Statistical guidelines for early stopping of the CAPT will be presented by the Coordinating Center and accepted or modified as the Committee chooses. Recommendations for protocol change are based on the majority opinion of the Data and Safety Monitoring Committee. A minority opinion may be prepared at the discretion of the dissenting members of the Committee. Recommendations on major changes in the study protocol are forwarded to the National Eye Institute for final approval. A Medical Monitor chosen from among the Committee members reviews summaries of adverse events. The Committee will provide a summary report concerning their review of adverse events once a year to the local institutional review board (IRB) associated with each clinical center.

### 3.5.3. Meetings

The Chair of the Data and Safety Monitoring Committee convenes this group for a face-to-face meeting at least once a year to review the special Data and Safety Monitoring Reports prepared by the Coordinating Center. The Committee also meets via a telephone conference call on an annual basis, between in-person meetings. Any member of the Committee may request a meeting if he/she believes the data in an interim report warrant such a meeting.

## 3.6. CLINIC MONITORING COMMITTEE

The Clinic Monitoring Committee is responsible for the quality assurance activities required to maintain standardization of procedures and adherence to the Study protocol in the clinical centers. The Committee will act in accord with the guidelines on data integrity put forth by the NEI in Spring 1994 and with established standards for certification of clinic staff and timeliness of activities. (Knatterud, 1998).

### 3.6.1. Membership

The Project Director of the Coordinating Center chairs the Clinic Monitoring Committee. Other members include the Director of the Coordinating Center, the Protocol Monitor, the Systems Analyst, the Director of the Reading Center, and other individuals with special expertise in clinic management, vision assessment, and quality assurance methodology. No term of membership is specified. The Study Chair is an *ex officio* member of this committee.

### 3.6.2. Functions

Some of the specific functions of the Clinic Monitoring Committee are:

- To visit each clinical center early in the enrollment phase in order to assure that all required equipment and facilities meet Study criteria and that the required staff members have been recruited and trained in the Study protocol;
- To visit each clinical center periodically during subsequent years in order to review operations, to certify new staff, and to review any special problems and explore ways to correct them;
- To monitor visual function data for unexpected patterns that suggest problems in measuring or recording the data;
- To maintain the certification program for clinic staff, following the criteria approved by the Executive Committee;
- To certify visual acuity lanes when changes are made in clinic facilities;
- To communicate with each Clinic Coordinator quarterly to review staff changes and clinic problems;
- To schedule and organize training sessions for participating ophthalmologists, Clinic Coordinators, Visual Function Examiners, and photographers, as required;
- To place on the agenda of the Executive Committee clinic problems for which corrective action is required or to which extraordinary resources of the Coordinating Center or Reading Center have been diverted;
- To place on the agenda of the Data and Safety Monitoring Committee any clinic problems that may compromise the accuracy or the quality of data reported.

### 3.6.3. Meetings

The Clinic Monitoring Committee meets before each Data and Safety Monitoring Committee meeting to formally review quality control procedures. Telephone calls and written communications are used to transact committee business between meetings.

### 3.6.4. Protocol Monitor

The role of the Protocol Monitor is one of the responsibilities of the Research Assistant. This person is responsible for reviewing adherence to the Study Protocol and evaluating each clinic's effectiveness in attaining Study goals. The Protocol Monitor observes clinic operations during regularly scheduled site visits, prepares written reports, and discusses observations with the Executive Committee as well as with the clinic staff. This individual is a key member of the Clinic Monitoring Committee.

### 3.7. COORDINATING CENTER

The Coordinating Center has the responsibility to ensure that the provisions of the *Manual of Procedures* (the operational version of the Study protocol) are carried out by all participating units. The Coordinating Center has an important role in the design, implementation, and execution of the Study trials. Staff members of this center have the primary responsibility for the development of the statistical design, development of operational and analytical methodology, and analysis of all data.

#### 3.7.1. Location and Staff

The CAPT Coordinating Center is administratively and operationally distinct from other CAPT centers located within the Scheie Eye Institute, Department of Ophthalmology of the University of Pennsylvania. Statistical, epidemiologic, and data processing expertise are provided by Coordinating Center staff through the Department of Ophthalmology. Consultants' services are used to supplement the staff for appropriate specialized tasks. Investigative and clerical personnel are employed to collect, process, and analyze the data for CAPT.

#### 3.7.2. Functions

The collection, processing, and analysis of all data are the primary responsibilities of the Coordinating Center. Some of the specific functions of the Coordinating Center investigators and staff are:

- To prepare and to maintain an up-to-date detailed Manual of Procedures with the guidance and consent of the Executive Committee and to revise the Manual of Procedures when approved by the Executive Committee;
- To work with the investigators in the development and testing of forms and procedures, and to assume responsibility for the reproduction and distribution of all CAPT forms;
- To make a random assignment of each eye enrolled in the CAPT to treatment or observation;
- To receive, process, and store the readings for each set of fundus photographs and fluorescein angiograms;
- To receive and store all data transmitted on the CAPT forms by the participating Clinical Centers;
- To monitor all Clinical Centers for adherence to the CAPT protocol;
- To check on the completeness and quality of all data and to periodically send out reports to participating clinics on delinquent forms, incomplete forms, etc.;
- To transfer the information recorded on paper forms to machine readable media and to develop and maintain a computer storage system for these data;

- To prepare at periodic intervals detailed analyses of the accumulated data in order to monitor for adverse and beneficial treatment effects;
- To prepare annual reports on the status of the CAPT for the National Eye Institute;
- To prepare reports for publication in collaboration with the clinical investigators;
- To prepare and distribute reports on the performance of the participating clinics;
- To prepare and distribute patient recruitment and retention aids for use at the Clinical Centers;
- To visit each of the Clinical Centers at regular intervals;
- To assist in training Clinic Coordinators in CAPT procedures;
- To receive all information pertinent to CAPT from the Clinical Centers and the Reading Center.

In general, the Coordinating Center is responsible for coordinating and/or organizing all CAPT activities involving the Coordinating Center, the Clinical Centers, the Executive Committee, the Clinic Monitoring Committee, and the Data and Safety Monitoring Committee. See Chapter 18 for a detailed discussion of Coordinating Center procedures and responsibilities during each phase of the CAPT.

### **3.8. READING CENTER**

The CAPT Reading Center is responsible for the evaluation of retinal photographs of all patients entered into the Study to determine eligibility of the patients, compliance with the treatment protocol, and follow-up status of eyes of all Study patients.

#### **3.8.1. Location**

The Reading Center, like the Coordinating Center, is a functionally and operationally separate unit within the Scheie Eye Institute, Department of Ophthalmology of the University of Pennsylvania.

#### **3.8.2. Functions**

Some of the specific functions of the Reading Center are as follows:

- To determine on the basis of photographs whether eligibility criteria for entrance into the CAPT have been satisfied and whether treatment was performed according to the protocol;
- To notify the responsible clinic directly if a patient is declared ineligible on the basis of photographs;
- To evaluate retinal photographs of all CAPT patients to determine the follow-up status of CAPT eyes;



- To determine the eligibility of a patient prior to randomization at the request of a clinic;
- To certify treating ophthalmologists and photographers as competent in the protocol procedures;
- To produce and distribute to the clinics materials to aid CAPT ophthalmologists in adhering to treatment protocol.
- To assess the quality of color fundus photographs and fluorescein angiograms;
- To notify the Coordinating Center if a clinic fails to adhere to the treatment or photography protocol;
- To receive and store all fundus photographs and fluorescein angiograms of CAPT patients.

See Chapters 14 and 17 for a detailed discussion of Reading Center procedures.

### **3.9. CLINICAL CENTERS**

Each center responsible for enrolling and treating patients in CAPT is known as a Clinical Center and is supported by a separate subcontract with the Coordinating Center through a grant from the National Eye Institute.

#### **3.9.1. Clinical Center Staff**

Each clinic is headed by a Principal Investigator who is an ophthalmologist and who represents the clinic at meetings of the Investigative Group. The professional and clerical organization of each Clinical Center differs, but each clinic has one person designated as the *Clinic Coordinator* who is responsible for having a thorough knowledge of the protocol, keeping changes in protocol and procedures up-to-date, ensuring that all non-protocol events within the clinic are properly documented, maintaining patient interest and participation in the study, seeing that the proper forms are accurately completed and the correct complement of required photographs are taken and sent to the Reading Center, and handling communications regarding data collection and processing with the staff of the CAPT Coordinating Center. Each center also has at least one Visual Function Examiner who is not the Clinic Coordinator to provide for the masked evaluation of visual acuity, contrast threshold and reading.

#### **3.9.2. Clinical Center Functions**

The function of each of the clinical centers is to carry out the provisions of the *Manual of Procedures* at the local level. Each clinical center is responsible for recruitment of an adequate number of patients and for follow-up of all patients until the Data and Safety Monitoring Committee and the Executive Committee decide that continued follow-up is no longer necessary. See Chapter 7 for additional operational aspects of the clinical center staff.

## CHAPTER 4

### STUDY POLICY

#### 4.1. PATIENT CONSENT

Written informed consent must be obtained from each patient prior to enrollment into CAPT. The consent form is prepared locally based on a prototype provided by the Coordinating Center and is submitted to the local institutional review board for approval before CAPT patients are enrolled. A copy of the approved form is sent to the Coordinating Center.

The patient should be asked to sign the consent form only after the patient has been introduced to the study and had questions answered to his or her satisfaction. In most clinical centers where color stereo photography and fluorescein angiography are not part of typical care of patients with bilateral drusen, the consent form should be signed after visual function testing and the ophthalmologic review and before photography. The signed consent form must be kept in the clinic and may be inspected during site visits. The Data and Safety Monitoring Committee may review consent forms from time to time to assure adherence to minimum standards established by that committee.

#### 4.2. PATIENT COSTS

Grant funds are not sufficient to pay all costs for all patients. Charges for photography and treatment can be handled through a combination of charging third party payers, the patient, and the study funds. Standard of care varies by region of the country and is interpreted differently by different insurers. NEI is not providing funds for either the initial treatment or the treatment at 12 months. In some areas, an annual fluorescein angiogram for these high-risk patients is within the realm of standard of care. Annual color photographs may be considered standard care in some situations. If funds for photography are requested through subcontracts to clinical centers, the charge by the clinical center is approximately equal to the Medicare reimbursement level. Professional fees for examinations and photography may be charged to the patient or waived at the discretion of the local investigator.

#### 4.3. PUBLICITY

All publicity and press releases on behalf of CAPT are to have prior approval of the Executive Committee. CAPT investigators who are approached by the press for information concerning CAPT should refer these inquiries to the Information Office of the National Eye Institute. It is recognized that when information is sought from an individual investigator by the local press in his or her own community, it is sometimes necessary or desirable for the investigator to handle the request him/herself. In such an event, the participating investigator who gives information should speak as an individual and not as the official representative of CAPT. This fact should be made clear to the press; however, the information given should be accurate and reflect the general policy and views of the group.

#### **4.4. EDITORIAL POLICY**

The Executive Committee establishes writing committees for CAPT papers from among the CAPT Investigative Group. CAPT papers are defined as those that use data, documents, or other information collected during the course of CAPT. Investigative Group members are invited to volunteer for these writing assignments and to suggest additional topics where appropriate.

The Executive Committee reviews all written reports prepared for publication. All reports from the Complications of Age-related Macular Degeneration Prevention Trial Group that involve comparison of treatment groups and/or the major outcome measures of CAPT will list the "Complications of Age-related Macular Degeneration Prevention Trial Group" as author. All professional participants of the Group are listed at the end of each paper and are considered as contributors. In addition, all CAPT personnel, past and present, may be listed with the approval of the principal investigator for whom they have worked. With the approval of the Executive Committee, publications may list members of the writing team in a footnote on the title page.

Papers prepared for publication must be sent to the CAPT Chairman or to the Coordinating Center Director for review by the Executive Committee. Each publication must acknowledge National Eye Institute support.

Oral presentations of more than local scope must be approved in advance by the Executive Committee. Abstracts to be printed must be approved by the Executive Committee. No unpublished study results may be used for oral presentations, local or otherwise, unless the Executive Committee grants a specific exception. The above restrictions do not apply to local presentations on the design of the CAPT, provided these presentations contain no unpublished CAPT results. Such presentations are encouraged to stimulate recruitment.

Copies of CAPT papers are sent to all principal investigators as well as members of the Executive Committee and the Data and Safety Monitoring Committee (DSMC) for information before publication. Reprints of published papers are mailed to each center for distribution among the staff and to outside consultants, including the members of the DSMC.

Manuscripts emanating from ancillary studies must be sent to the Executive Committee for review before submission for publication. See also Section 4.5.

#### **4.5. ANCILLARY STUDIES**

##### **4.5.1. Introduction**

Individual investigators who wish to carry out ancillary studies are encouraged to do so. It is believed that such ancillary studies may greatly enhance the value of CAPT and insure the continued interest of many capable investigators. However, to protect the integrity of CAPT, such ancillary studies must be reviewed and approved by the CAPT Executive Committee and Data and Safety Monitoring Committee before their execution, whether or not they involve the need for supplementary funds.

#### **4.5.2. Definition of an Ancillary CAPT Study**

An ancillary study is a research study that requires either

- Supplementary observations or procedures to be performed upon all or a subgroup of the CAPT patients according to a set protocol, or,
- Additional effort or activity by either the Coordinating Center or the Reading Center staff beyond the current scope of CAPT.

#### **4.5.3. Reasons for Requirement of Approval**

Everyone concerned with CAPT is entitled to prior assurance that no ancillary study will:

- Complicate the interpretation of the CAPT results;
- Adversely affect patient cooperation;
- Jeopardize the public image of the CAPT;
- Create a serious diversion of CAPT resources locally, at the Coordinating Center, or at the Reading Center.

#### **4.5.4. Preparation of Request for Approval of an Ancillary CAPT**

The request for approval of an ancillary study should be in narrative form. It should contain a brief description of the objectives, methods, and significance of the study. Full details should be given concerning any procedures to be carried out on any CAPT patients, such as visual function tests, psychiatric interviews, psychological testing, radiological procedures, venipuncture, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be performed on a patient outside of the clinic should be described. Mention should be made of the extent to which the ancillary study will require extra clinic visits by the patient or will lengthen the patient's usual clinic visits.

#### **4.5.5. Procedures for Obtaining Ancillary Study Approval**

The investigator concerned should send the ancillary study request to the Director of the Coordinating Center for distribution to all members of the Executive Committee. Within a reasonable time, the Director will summarize any questions and/or objections raised by members of the Executive Committee and send this summary to the applicant so that he/she may amplify, clarify, and/or withdraw the request. The members of the Executive Committee will then have another opportunity to review the request. The Director of the Coordinating Center then prepares a statement of the Executive Committee consensus, including any remaining reservations or objections. This statement is forwarded to the investigator who requested approval for the ancillary study. After Executive Committee approval is obtained, the information is then forwarded to the DSMC for its approval.

#### **4.5.6. Funding of Ancillary Studies**

If no additional funds are required, the investigator may proceed with the ancillary study as soon as the Executive Committee and Data and Safety Monitoring Committee approve it. If additional funds are needed, the investigator may prepare and submit a new research grant application to the Division of Research Grants, National Institutes of Health, or any other potential sponsor, for review in the same manner as any other new research grant application. It is understood that the investigator is not to accept the grant or activate the ancillary study until approval has been received from the CAPT Executive Committee and DSMC.

#### **4.5.7. Publication of Ancillary CAPT Results**

All manuscripts or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the CAPT Executive Committee before publication or presentation. Such review will pertain to the expected impact on CAPT objectives and not to scientific merit alone. Appropriate acknowledgment of the CAPT resources used—whether data, patients, or CAPT investigators— should be included.

#### **4.5.8. Progress Reports to Executive Committee**

The investigator of each approved ancillary study is required to provide a written progress report for review by the Executive Committee at each scheduled meeting. The Coordinating Center reminds the investigators of the deadline and collects progress reports for distribution to the Executive Committee.

### **4.6. RELATED STUDIES**

Individual CAPT investigators who carry out studies related to ongoing, completed, or proposed CAPT substudies should be aware that their conclusions and interpretations might be viewed by non- CAPT investigators as reflecting the position of the CAPT Group. The study may be related because of types of patients included, types of treatment evaluated, or similarity of methods to those used in CAPT. Therefore, investigators are encouraged to submit reports from related studies to the Executive Committee for review prior to presentation or submission for publication in order to assure that the goals of the CAPT are not jeopardized.

## CHAPTER 5

### ELIGIBILITY CRITERIA

#### 5.1. INTRODUCTION

In referring to the eyes of patients enrolled in the CAPT *both eyes are study eyes*. Eligibility criteria are designed to be as inclusive as possible in order to maximize generalizability of the results without jeopardizing the ability to observe a treatment effect because of interfering causes of visual loss.

#### 5.2. ELIGIBILITY CRITERIA

##### 5.2.1. Eligibility criteria for all patients

**Patients** must meet the following criteria for entry into the CAPT:

- Age  $\geq$  50 years
- Signed informed consent form
- No condition that precludes follow-up for 5 years.

Clarification of these criteria follows:

**AGE:** Few patients below the age of 50 are anticipated to meet the criteria below of having at least 10 large drusen in each eye. Patients below the age of 50 may have forms of macular degeneration other than age-related macular degeneration.

**RACE:** Bilateral legal blindness from the complications of AMD is rare among African Americans. However, little is known about the risk of other levels of vision loss among African American patients who have 10 or more large drusen in each eye.

**INFORMED CONSENT:** Written informed consent must be obtained from each patient prior to enrollment into CAPT. The patient should be asked to sign the consent form only after the patient has been introduced to the study and had questions answered.

**HEALTH STATUS:** Patients must have a high probability of completing 5 years of follow-up. The mere presence of serious health conditions such as hypertension, cardiovascular disease, and cancer in this population does not disqualify the patient from enrollment. However, if the severity of the condition is such that progression to a state where travel to the clinical center for regular follow-up visits would place undue burden on the patient or is such that death is almost certain to occur during the follow-up period, the patient should not be enrolled in the study. Patients with known plans to move to an area of the country without a nearby CAPT clinical center should not be enrolled.

### 5.2.2. Eligibility criteria for study eyes

**Study eyes** must meet the following criteria for entry into the CAPT:

- 10 or more large drusen (>125 microns) within 3000 microns of the foveal center
- Visual acuity of 20/40 or better
- Disc and macula color photographs and fluorescein angiogram within 28 days of randomization.
- Total area of geographic atrophy within 3000 microns of the foveal center must be  $\leq 1$  MPS Disc Area
- No geographic atrophy within 500 microns of the foveal center
- No serous PED of any size
- No evidence of exudative AMD now or in the past
- No cryotherapy, laser retinopexy or retinal detachment repairs within the last 3 years.
- No vitrectomy within the last 12 months.
- No LASIK surgery within the last 12 months or if the pre-surgical refractive error was  $< 8$  diopters of myopia or there are pathologic retinal changes related to high myopia.
- No lens extraction or implantation within the last 3 months
- No capsulotomy within the last 3 days
- No lens or other media opacity that would preclude good fundus photography or angiography within the next 5 years
- No nevus  $> 2$  disc areas within 3000 microns of the foveal center or with fluid or leakage on fluorescein angiography.
- No macular edema or signs of diabetic retinopathy more severe than 10 red dots (microaneurysms or blot hemorrhages)
- No retinal changes related to high myopia and no myopic correction greater than 8.00 diopters spherical equivalent [sphere +  $\frac{1}{2}$  cylinder]
- No progressive ocular disease that would affect visual acuity within the next 5 years
- No current use or history of using macular affecting drugs beyond levels specified below.

Some clarifications of these criteria follow:

**DRUSEN:** Drusen must have a diameter of at least 125 microns to be count towards the number of drusen required for eligibility. Eyes that exceed the minimum number of drusen are most desirable. Eyes with basal laminar drusen are not eligible.

**FOCAL HYPERPIGMENTATION:** Focal hyperpigmentation is not an explicit requirement. Small areas of focal hyperpigmentation are present commonly in eyes with multiple large drusen.

**VISUAL ACUITY SCORE:** The visual acuity score for a study eye must be greater than or equal to 43 letters. In most cases, this means reading at least 3 letters on the 20/40 line of the visual acuity chart at a distance of 3.2 meters.

**PHOTOGRAPHS:** Stereoscopic color photographs of the disc and macula of each eye are required. A fluorescein angiogram with the early phase including both eyes is also required. Color photographs and the fluorescein angiogram must be taken within 28 days of randomization.

**GEOGRAPHIC ATROPHY:** Eyes with areas of geographic atrophy within 3000 microns of the foveal center are eligible only if the total area of geographic atrophy is  $\leq 1$  MPS disc area and there is no geographic atrophy within 500 microns of the foveal center. Geographic atrophy is defined as one or more sharply defined, more or less circular patches of partial or complete depigmentation of the RPE, which typically exposes choroidal blood vessels. To be classified as geographic atrophy, a patch must have an area greater than or equal to a circle with a 250 micron diameter.

**RETINAL PIGMENT EPITHELIAL DETACHMENT (PED):** Eyes with a serous detachment of the pigment epithelium are considered to have exudative AMD and are not eligible for CAPT. Eyes with a "drusenoid PED" (an uneven elevation of the retinal pigment epithelium overlying an area of confluent drusen) are not considered to have exudative AMD and are eligible for the study. The CAPT Reading Center will provide an interpretation of an angiogram concerning the type of PED present upon request.

**EVIDENCE OF EXUDATIVE AMD:** Active occult or classic CNV as defined by leakage of dye on fluorescein angiography, as well as a serous PED, makes an eye ineligible. Also, a disciform scar and/or laser treatment scar makes an eye ineligible.

**CATARACT SURGERY:** Eyes that have had lens extraction or lens implantation within the last 3 months are ineligible. Eyes that have had a capsulotomy within the past 3 days are ineligible.

**LENS OPACITIES:** Lens opacities may be present but must be such that at enrollment and for the next 5 years the visual acuity would be expected to be 20/40 or better and the view of the posterior pole for ophthalmoscopy, photography, and laser photocoagulation is unobstructed.

**DIABETIC RETINOPATHY:** Eyes with 10 or fewer red dots (microaneurysms or blot hemorrhages) are eligible for the study. However, if an eye has 11 or more red dots within 3000 microns of the foveal center or has any sign of more advanced retinopathy, as defined on the Wisconsin Diabetic Retinopathy grading scale, the eye is ineligible. An eye with macular edema is ineligible for the study. Photographs of the seven DRS Standard Photographic Fields are not required for diabetic patients.



**MYOPIA:** Eyes with fundus changes consistent with high myopia, such as lacquer cracks, are ineligible. Eyes with a spherical equivalent more negative than -8.00 diopters are ineligible even if there are no myopic changes apparent in the fundus.

**PROGRESSIVE OCULAR DISEASE:** Any condition that is likely to decrease visual acuity over the course of 5-years excludes the patient from the study. Eyes with non-progressive ocular diseases unlikely to affect vision within 5 years require prior approval from the CAPT Reading Center.

**GLAUCOMA:** Eyes with glaucoma are eligible for the study if there is a low likelihood of loss of central vision within the next 5 years. Patients with ocular hypertension only are eligible. See the section on macula affecting drugs concerning the use of some drugs commonly used in the treatment of glaucoma or ocular hypertension.

**MACULA AFFECTING DRUGS:** Patients taking systemic steroids, Mellaril (thioridazine), Aralen (chloroquine), or phenothiazide derivatives are not eligible. History of use of the drugs in the distant past does not necessarily exclude the patient if the CAPT ophthalmologist verifies that there has been no ocular damage as a result. A lifetime dose of 100 gm of chloroquine or past regular use of 500 mg per day of Mellaril or 1000 mg of Thorazine (chlorpromazine hydrochloride) excludes the eye from the study. If, after consultation with the patient's internist, a patient can be changed from systemic steroids to alternative medication, the patient is eligible for the study after 30 days of no systemic steroid use.

In addition, patients currently using Xalatan (latanoprost), Propine (dipivefrin), or epinephrine are ineligible for the study. If, after consultation with the patient's ophthalmologist, a patient can cease taking these medications, the patient is eligible for the study after 30 days.

### 5.3. PRE-RANDOMIZATION REVIEW OF PHOTOGRAPHS FOR ELIGIBILITY

It is expected that CAPT ophthalmologists will determine patient eligibility for CAPT. However, Reading Center staff are available to review photographs submitted from centers prior to a patient's enrollment in CAPT. The purpose of pre-randomization review is to assist with the interpretation of photographs of borderline-eligible cases and to assist ophthalmologists in identifying the presence of exclusion criteria. Refer to Section 15.13 for details on how to obtain a pre-randomization review.

## CHAPTER 6

### TREATMENT

#### 6.1. EVOLUTION OF CAPT PREVENTIVE LASER TREATMENT

The treatment protocol used in CAPT evolved from the methods used by early investigators of preventive laser treatment and the experience from the pilot study for CAPT, the Choroidal Neovascularization Prevention Trial (CNVPT) as summarized in Chapter 1.8, 1.11, and 1.12.

#### 6.2. TREATMENT OF PATIENTS

The laser protocol used in CAPT consists of initial treatment immediately after randomization and additional treatment at 12 months, dependent on resolution of drusen (see Exhibit 6-1). Initial treatment consists of 60 burns using a 100 micron spot size in a grid pattern. Treatment is within a doughnut-shaped area between 1500 and 2500 microns from the foveal center. The desired intensity is a barely visible (not white) lesion. (A photographic standard demonstrating the desired intensity is available from the CAPT Reading Center.) Fifteen burns are applied per quadrant without regard to drusen, (i.e., no effort will be made to hit or avoid drusen) but avoiding retinal blood vessels. Only topical anesthesia (eye drops) is required.

##### 6.2.1 12-Month Treatment of Patients

Treatment is again performed at 12 months if 10 or more large drusen remain or if there is an area of drusen (greater than  $63\mu$ ) that is equivalent to the area of 10 CAPT drusen within 1500 microns of the foveal center. Treatment should not be applied in the following circumstances: 1) exudation (CNV or S-PED) was present at baseline or has developed in either eye, 2) geographic atrophy is present within  $500\mu$  of the foveal center of the eye assigned to treatment, or 3) new geographic atrophy has developed greater than 1 disc area in the eye assigned to treatment. If the patient was enrolled with basal laminar drusen, pathologic myopia or pattern dystrophy, treatment should not be performed at 12 months.

Thirty burns will be administered in the 1000 and 2000 microns annulus centered on the fovea. Drusen will be treated directly. If all drusen within 1000 and 2000 microns of the foveal center can be treated with less than 30 burns, the remainder of the burns will be applied evenly within the annulus of treatment, avoiding retinal vessels.

For both initial treatment and 12-month treatment, the power level of the argon green laser should be first set at approximately 90 milliwatts and adjusted depending on the particular characteristics of the laser and the patient to achieve a barely visible (not white) lesion.

### 6.2.1 Contact Lenses and Spot Size Settings for CAPT Treatments

For both the initial and 12-month CAPT treatment, a flat contact lens should be used with a spot size setting that produces a 100 $\mu$  spot on the retina. The following lenses are appropriate for CAPT treatment when used with the setting specified below. Clinic coordinators or ophthalmologists should contact the Coordinating Center before using a contact lens not listed below.

<u>Contact Lens</u>	<u>Setting to produce a 100<math>\mu</math> spot on retina</u>
Goldmann Lens	100 $\mu$ setting on laser
Mainster Standard	100 $\mu$ setting on laser
Volk Area Centralis	100 $\mu$ setting on laser
Haag Streit 64.5 D	100 $\mu$ setting on laser
Ocular Instruments Plano Lens	100 $\mu$ setting on laser
Panfundusopic	75 $\mu$ setting on laser
Volk TransEquator	75 $\mu$ setting on laser
Mainster Wide Field	75 $\mu$ setting on laser
Volk QuadrAspheric	50 $\mu$ setting on laser
Mainster Ultra Field PRP	50 $\mu$ setting on laser
Volk SuperQuad 160	50 $\mu$ setting on laser
Volk SuperMacula 2.0	200 $\mu$ setting on laser

### 6.3. RATIONALE FOR LASER TREATMENT PROCEDURE

As noted in Chapter 1, a number of different treatment techniques have been proposed. The issues to be addressed are the location, number, and intensity of burns; whether to treat drusen directly; and whether additional treatment should be applied. While the exact relationship among drusen and the development of CNV is not known, it is known that drusen are not localized pockets of pathology but are indicators of a diffuse thickening of the inner aspect of Bruch's membrane. Large drusen do not appear to be discrete stimuli in and of themselves for the ingrowth of new vessels, unlike histo spots (MPS ; 1996).

#### 6.3.1. Location of burns

The location of burns should be designed to promote drusen resolution throughout the macula and to minimize potential complications of laser treatment. Treating 360° around the foveal center provides the effect of the laser treatment throughout the macular area. Restricting burns to no closer than 1500 microns from the foveal center for the initial treatment and 1000 microns for treatment at 12 months decreases the risk of loss of critical central vision from the laser burns themselves, from possible subsequent atrophy, and from stimulation of new vessels in the parafoveal area. The grid pattern of the initial treatment allows the entire macular region to be affected by the laser treatment. Experience from the CNVPT and the other pilot studies of laser treatment suggest that some resolution of drusen should be expected within the 1500 micron circle around the foveal center despite the absence of direct

treatment. Treatment somewhat closer to the foveal center (inner bound 1000 microns for retreatment vs. 1500 microns for initial treatment) at 12 months should provide a stronger stimulus for drusen reduction since drusen resolution has been shown to be more complete closer to the area of direct treatment. (CNVPT 1998; Sigelman, 1991; Figueroa, 1994).

### **6.3.2. Number of burns**

The number of burns should promote widespread resolution of macular drusen. Previous pilot studies have used anywhere from 6 to well over 500 burns. The average number of burns was 100 (range:51 to 154) in the study by Frennesson and Nilsson and 132 (range 23 to 516) in the Little study. This number of burns had no apparent deleterious side effects. We estimate that an initial 60 burns, with the addition of 30 if there is not nearly complete resolution of drusen, will allow sufficient coverage to the area within 2500 microns of the foveola.

### **6.3.3. Intensity of burns**

Drusen have regressed after both intense photocoagulation of CNV and after light, barely visible burns. If a similar effect can be achieved with a low intensity burn as with a high intensity burn, the low intensity burn is preferred since it will cause less damage to the photoreceptors than a heavy burn, may be less likely to induce the late development of atrophy around the treatment scars, and may be less likely to induce CNV. The intensity of the burns was correlated with the development of CNV in the Fellow Eye Study of the CNVPT. At ARVO 1997, Joseph Olk, MD reported more CNV in the threshold intensity diode laser treatment group than in the subthreshold intensity diode laser group of the IRIS Medical clinical trial. CAPT investigators have chosen a very low intensity burn for CAPT: a barely visible (not white) lesion.

Test burns may be applied to establish the appropriate power setting to achieve the burn intensity specified in the treatment protocol. Test burns should be applied just outside the area designated for treatment. Record both the number of test burns and the number of burns applied within the area designated for treatment on the treatment data collection forms. The power setting may be adjusted during the treatment, but should not be increased if treating over a druse.

### **6.3.4. Treatment of drusen**

For the CNVPT, drusen were not treated directly because investigation of the remote effect of laser was of interest. However, most of the other groups studying drusen have either treated drusen directly with laser or have treated the macula in a specific grid laser pattern. There have been no reports of harm stemming from the direct treatment of drusen. For the first treatment, when the intent is to have an effect on a widespread area of the macula, treatment is applied in a grid pattern, regardless of the location of the drusen. For treatment at 12 months, when the intent is to hasten the resolution of remaining drusen within 1500 microns of the foveal center, treatment is applied directly to drusen.

### 6.3.5. 12-Month Treatment

Since the mechanism by which the laser treatment may be protecting the eye from advanced forms of AMD is not known, only an indirect indicator of when the eye has experienced a treatment effect (reduction of drusen) can be used. Failing to pursue additional reduction of drusen when they persist in the central macula could lead to showing no effect on reduction of risk of vision loss because too little treatment has been applied. Thus, laser treatment of persistent drusen will be performed at 12 months.

Complications of laser photocoagulation of the retina have included stimulation of new vessels, subretinal fibrosis, macular pucker, scotomas, and late loss of visual acuity from progressive atrophy. Most of these complications have been associated with burns that were much more intense than those proposed for CAPT, such as those used for treating CNV. Progressive atrophy causing visual loss years after treatment has been associated with the lighter burns used in the grid treatment of diabetic macular edema (Schatz, 1991). Eleven of 203 (5%) consecutive cases developed progressive enlargement of atrophy. However, the intensity of those burns was greater (light to medium light burn), the spacing of the burns was closer (100 to 200 microns apart), and the proximity of the burns was closer to the foveal center.

There have been relatively few complications reported with prophylactic laser treatment other than the very important complication of an increased rate of CNV within at least the first two years of treatment in fellow eyes of CNVPT patients. No immediate complications from treatment such as retinal or choroidal hemorrhage have been recorded among the 304 treatment sessions in the CNVPT. One patient with basal laminar drusen treated in San Francisco before the CNVPT (Hyver, 1997) and one patient with basal laminar drusen treated within the CNVPT lost vision after developing a vitelliform-like lesion and subsequent geographic atrophy in the foveal center. Susan Bressler, M.D. has reported verbally that geographic atrophy has developed in the area of treatment within 2 years of some of the approximately 30 patients treated in a pilot study in which the number of burns was sometimes over 200. Dr. Peep Algvere has reported verbally that 13 treated vs. 7 observed eyes of 32 bilateral drusen patients have developed areas of geographic atrophy by 4 years. However, the distribution of visual acuity in the two treatment groups is similar. Two of the eyes treated in the CNVPT had developed geographic atrophy in the area of treatment by 12 months. There were *no reports of these side effects* from the Spanish study (Figuerola, 1994), the Swedish study (Frennesson, 1995), the case report by Sigelman (1991), the study of Wetzig (1988), or Cleasby (1979). The follow-up periods in some of these studies were short and/or the methods of ascertainment were imprecise. These risks have been described in the prototype CAPT informed consent statement.

### **6.3.6. Determination of Need for 12-Month Treatment**

The participating ophthalmologist at each clinic determines if a patient is eligible for CAPT treatment at 12 months. The Reading Center provides clinical centers with a checklist to aid ophthalmologists in this decision. If the ophthalmologist believes that the patient is on the border of the eligibility criteria for additional treatment, the decision should be made to treat. The Reading Center will review the 12-month photographs of each CAPT patient. If the Reading Center's interpretation is that the eye should have been treated but treatment was not performed, the Reading Center will send a letter to the clinic requesting the patient be recalled and additional treatment performed. CAPT 12-month treatment should be performed within 15 months of the initial visit.

### **6.4. MANAGEMENT OF PATIENTS WHO DEVELOP CNV**

All patients will be advised verbally as well as in the CAPT patient informed consent form of the early visual symptoms of neovascular AMD and instructed to call the CAPT center immediately if they notice a change in their vision. Detailed retinal examinations will be performed at each scheduled clinic visit to detect newly formed CNV. Patients who develop CNV in an eye will be evaluated promptly for treatment of the CNV. If the lesion is amenable to laser treatment, or any proven treatment for established CNV that may emerge during the course of the study, the patient will be informed of his/her management options. Patients who reach this secondary endpoint will continue to be followed within CAPT for effects on their visual function and quality of life. Annual fluorescein angiograms are required for patients who develop CNV, as well as for all CAPT patients.

## EXHIBIT 6-1

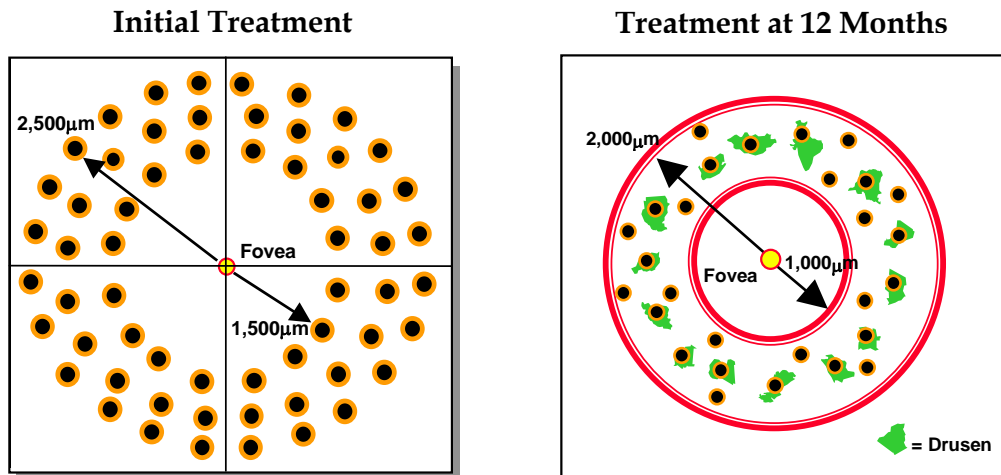
### Laser Treatment Summary (as of 7/5/00)

#### Initial treatment session

- **Number:** 60
- **Wavelength:** Green
- **Intensity:** Light intensity, 0.1 sec duration (barely visible, not white lesion)
- **Spot size:** 100 micron spot size
- **Configuration of burns** - grid; 15 burns per quadrant; avoiding retinal blood vessels
- **Location** - Burns should be placed:
  - 360 degrees, **centered on the foveal center**
  - No closer than 1500 microns from foveal center
  - No farther than 2500 microns from foveal center

**Treatment at 12 months** if  $\geq 10$  CAPT drusen ( $>125 \mu$ ) or an area of drusen ( $>63 \mu$ ) equivalent to the area of 10 CAPT drusen within 1500  $\mu$  of the foveal center.

- **Number:** 30
- **Wavelength:** Green
- **Intensity:** Light intensity, 0.1 sec duration (barely visible, not white lesion)
- **Spot size:** 100 micron spot size
- **Configuration of burns** - direct treatment of up to 30 remaining drusen; remainder of 30 burns after drusen treated are to be evenly spaced through the annulus of treatment, avoiding retinal blood vessels and areas of previous treatment (project a frame from the angiograms to identify burns from the initial treatment)
- **Location** - Burns should be placed:
  - No closer than 1000 microns from foveal center
  - No farther than 2000 microns from foveal center



## CHAPTER 7

### PATIENT VISITS, EXAMINATIONS, AND TELEPHONE CONTACTS

#### 7.1. INTRODUCTION

Each patient enrolled in CAPT is required to have visits to the CAPT clinical center and telephone contacts encompassing 5 years of participation (See Exhibit 7-1). Patients are enrolled in CAPT and treated in one eye during an Initial Visit. Follow-up Visits requiring testing of vision, clinical examination, and photography are scheduled for 6 months and then annually at 12, 24,36,48, and 60 months. Safety Check Visits are scheduled 3 months after each CAPT treatment to assess whether laser treatment has induced any adverse effects. Telephone calls are made by the Clinic Coordinator at 18, 30, 42, and 54 months to maintain active contact with the patient and to elicit information on any change in vision that the patient might have experienced since the last examination. At least one CAPT data collection form must be completed documenting each of the required visits and telephone contacts.

CAPT patients may be seen in the CAPT clinical center between their regularly scheduled visits. Patient are encouraged to call the Clinic Coordinator at any time a change in vision is noticed so that the patient may be scheduled for an examination in the clinical center to assess the cause of the change in vision and to offer treatment if indicated. Alternatively, the CAPT Participating Ophthalmologist may believe that examining the patient more frequently than required by the CAPT schedule is in the patient's best interest. No data collection form is required for these extra visits unless an exudative event (choroidal neovascularization [CNV] or serous pigment epithelial detachment [S-PED]) is detected and confirmed by fluorescein angiography.

The first observation of CNV or a serous PED in an eye is considered an exudative event requiring documentation with a Clinic Exudative Event Form, a Reading Center Exudative Event Form and a fluorescein angiogram (see Chapter 15). If the exudative event is first observed at a regularly scheduled follow-up visit, the usual complement of forms, photographs and a fluorescein angiogram are required in addition to the Exudative Event Forms.

If any study visit is missed and cannot be rescheduled within the time window printed on the patient's appointment schedule, a Missed Visit Form should be completed and mailed to the Coordinating Center. A blank slide sheet, as described in Section 15.4., should be sent to the Reading Center.

#### 7.2. INITIAL VISIT

The Initial Visit encompasses the activities of evaluating the patient for eligibility, recording of baseline information, enrollment into CAPT, randomized treatment assignment, and laser treatment. The order in which various procedures are performed may vary from clinic to clinic, subject to the restrictions discussed below.



### **7.2.1. Patient Identification**

Clinic Coordinators assign patients a permanent identification number and name code to be used on all CAPT forms and photographs. The patient identification number is a three-part identifier consisting of a two-digit clinic number, three-digit sequence number, and a final letter "C". The name code is a five-letter sequence consisting of the first two letters of the patient's first name, middle initial, and first two letters of the patient's last name. If the patient does not have a middle initial, a dash should be substituted for a letter.

Each patient is also identified with a site within a clinical center. The patient's site is identified by a two-digit clinic number followed by a single digit site number. The patient's site identifies the address that is used for sending all patient specific correspondence, such as edit queries and appointment reminders. At some point in follow-up, a patient may move from one site to another within a clinical center or from one clinical center to another. If the patient moves to another site or clinical center, a Transfer of Patient Form must be completed.

Patients are entered into the Patient Log with their ID number, name code, site number, and full name. The same information should be entered into the duplicate Patient Log (see Chapter 10).

### **7.2.2. Patient History**

Candidates for CAPT should have some indication that they have sufficient drusen in each eye from previous examinations, photographs, or referral by outside ophthalmologists. The Clinic Coordinator should review the questions on the history portion of the Initial Visit Form with the patient to make sure the patient is not ineligible because of prior history. Participation in other clinical trials is not an automatic exclusion; however, the Clinic Coordinator must call the Project Director of the Coordinating Center to discuss the treatment and follow-up required for any study that the patient is already participating in.

Clinic Coordinators must complete the Patient Information Form so that the patient can be traced if contact is lost later in follow-up. Completion of this form may be delayed until after eligibility has been established, but it must be completed before requesting a treatment assignment.

### **7.2.3. Testing Visual Function**

Refraction and testing of visual function must be performed before the patient's eyes are dilated and before fundus photography if these procedures are to be carried out on the same day. Refraction must precede all tests of visual function. Generally, visual acuity should be tested before testing contrast threshold or reading speed. If the Clinic Coordinator is also certified as a Visual Function Examiner, the Clinic Coordinator may perform the refraction and tests of visual function during the initial visit only. Standardized procedures, as described in Chapter 8 must be followed.

#### **7.2.4. Eye Examination**

The Participating Ophthalmologist performs a dilated eye examination of each eye of the patient to establish that the ocular inclusion criteria are met and that none of the ocular exclusionary conditions are present. If the patient is still eligible by the end of the examination, the ophthalmologist should introduce the study to the patient and answer questions by the patient and/or companions of the patient.

#### **7.2.5. Informed Consent**

Informed consent should be obtained before photography and before the patient completes the quality of life instruments. In many clinical centers, photography, especially angiography, and administration of the quality of life instruments would not be performed for patients outside of the study. The patient should not be asked to sign the form until either the Clinic Coordinator or the Participating Ophthalmologist has answered all questions.

#### **7.2.6. Quality of Life Questionnaire**

After the patient has signed the consent statement, the patient is asked to complete the quality of life questionnaire as described in Chapter 9. The Clinic Coordinator checks that all questions have been answered and that all answers are legible before completing the Eligibility Checklist.

#### **7.2.7. Photography**

A CAPT certified photographer takes stereo color photographs of the disc and macula of each eye and a fluorescein angiogram according to the standardized procedures described in Chapter 16. Photography must be performed after testing visual function if these procedures are carried out on the same day.

#### **7.2.8. Patient Enrollment and Randomized Treatment Assignment**

Patient enrollment and randomization are initiated when the Clinic Coordinator faxes a completed copy of the Eligibility Checklist to the Coordinating Center (fax number: 215-615-1531). The Clinic Coordinator should call the Coordinating Center's main telephone line (215-615-1500) to confirm that the fax was received and to arrange a time for treatment assignment. The telephone call to the Coordinating Center must be made by 5:00 P.M. Eastern Time, unless other arrangements have been made. All procedures involved in the Initial Visit must be performed within a **28-day** period. Thus, if color photographs, the fluorescein angiogram, or visual function testing are more than 28 days old, they must be repeated. The request for treatment assignment involves participation of the Clinic Coordinator and the Participating Ophthalmologist and follows the procedures outlined in Chapter 18.

### **7.2.9. Treatment**

Patients and ophthalmologists should be prepared to start laser treatment to the assigned eye immediately after randomization. A Treatment Form is completed using information provided by the treating ophthalmologist. The treating ophthalmologist is generally the ophthalmologist who enrolled the patient. Post-treatment color photographs of the macula of the treated eye are taken on the day of treatment. If it is impossible to take post-treatment photographs immediately after treatment, they may be taken *up to* 48 hours after treatment. The patient's eye will need to be washed to remove gel used during treatment. For post-treatment photographs to be gradeable, several rinses may be required to sufficiently remove the gel. (Refer to Section 16.5.2.1 on procedures to remove the gel.) Before leaving the clinic, the Clinic Coordinator schedules the patient for a Safety Check Visit at 3 months.

### **7.2.10. Checking the Forms for Completeness and Mailing**

The Clinic Coordinator should check that all questions on the left-hand side of the data collection forms are complete and that all indicated conditional questions are also complete. Names and certification numbers and dates for all portions of the form must be complete. Completed data collection forms should be sent to the Coordinating Center to the attention of the Data Coordinator (see CAPT Telephone and Address Directory). Forms should be mailed on at least a weekly basis. Initial Visit forms should be received by the Coordinating Center by 14 days after the completion of the visit. Photographic materials should be sent to the Reading Center according to the procedures in Chapter 15.

## **7.3. SAFETY CHECK VISITS**

Safety Check Visits are scheduled for 3 months after the Initial Visit for all patients and for 15 months for patients who are treated at FV12. The purpose of the visits is to assess the treated eye for adverse effects of laser treatment. The ophthalmologist examines the patient and a measurement of visual acuity is made. The measurement of vision is not for the purposes of data analysis; therefore, the examination does not need to be performed according to the CAPT protocol. No photographs are required unless there is suspicion of CNV, serous PED, or another retinal problem. A certified CAPT Participating Ophthalmologist must perform the dilated eye examination. The Safety Check Visit form is checked for completeness by the Clinic Coordinator.

## **7.4. REGULARLY SCHEDULED FOLLOW-UP VISITS**

Follow-up visits are scheduled for 6, 12, 24, 36, 48, and 60 months after enrollment into CAPT. The sequence of procedures generally follows the sequence outlined above for Initial Visits with a few important differences:

- The refraction and testing of visual acuity, contrast threshold, and reading must be performed by a masked Visual Function Examiner who is not the Clinic Coordinator for the patient. The Clinic Coordinator should supply the Visual Function Examiner with the patient's record of subjective refraction and the pages of the data collection form used to record the results of the refraction and testing of vision. The Clinic Coordinator should remind the patient that the Visual Function Examiner cannot be told which eye was treated and that the patient should make no comment about the treated eye or the treatment to the Examiner. The Reading test is re-administered only at Follow-Up Visits 36 and 60 months.
- The quality of life instrument is re-administered only at Follow-up Visit 60. The Clinic Coordinator explains to the patient that the interview can be administered by telephone if the patient has difficulty with self-administration because of vision or another physical condition. If the patient requires telephone administration, the Clinic Coordinator makes arrangements with the Research Associate in the Coordinating Center.
- The Clinic Coordinator asks the patient if any contact information has changed since the last visit to the clinic and updates the Patient Information form accordingly.

Fluorescein angiograms are required for all patients at each annual visit beginning with Follow-Up Visit 12. If there is angiographic evidence of either new serous PED  $\geq 1$  MPS disc area or new CNV in an eye, a Clinic Exudative Event Form and a Reading Center Exudative Event Form must be completed and sent to the Coordinating Center and Reading Center, respectively. Patients should be counseled about the availability of treatment. Confluent laser treatment or any treatment shown effective during the course of CAPT should be administered based on a decision by the CAPT ophthalmologist and the patient.

#### **7.4.1. Assessing Interim Medical History During Safety Check and Follow-up Visits**

The CAPT Safety Visit Form and Follow-up Visit Form collect data from the patient regarding their vision and any other ocular treatments that occurred since the patient's last CAPT visit. Either the clinic coordinator or CAPT-certified ophthalmologist may ask the patient these items. Visual function examiners are never to ask these items as the patient's response may jeopardize the visual function examiner's masking to treatment.

### **7.5. TELEPHONE CONTACTS**

Telephone calls by the Clinic Coordinator to the patient are required at 18, 30, 42, and 54 months. The purpose of the calls is to maintain personal contact with the patient and to remind the patient that he/she should call the Clinic Coordinator if there is a decrease in vision in either eye. A brief Telephone Visit form is completed to document the telephone call. Clinic Coordinators remind the patient of the scheduled date and time for the next regularly scheduled follow-up visit. Clinic Coordinators may choose to call the patient more frequently to maintain a good relationship with the patient. These telephone calls are not documented with a Telephone Visit form.

## **7.6. CHANGING THE SITE FOR PATIENT FOLLOW-UP**

During the course of their 5-year follow-up, some patients may choose to be seen at another CAPT-certified site within the clinical center. A Transfer of Patient Form must be completed so that materials relating to the patient are sent to the correct location. The patient's CAPT chart should be transferred to the new site.

Patients may move to another area of the country. If another CAPT clinical center is located closer to the patient's new home, a permanent transfer may be arranged and documented with Transfer of Patient Form. The CAPT staff at the new clinical center must accept responsibility for the follow-up of the patient before the patient can be transferred. The clinic coordinator and ophthalmologist from both clinics should sign the form indicating approval of the transfer, and send the completed form to the Coordinating Center. The clinic at which the patient was originally enrolled should copy the patient's CAPT chart and send it to the receiving clinic.

## **7.7. PATIENT DEATH**

As soon as clinic personnel become aware that a patient has died, a Patient Death form must be completed and sent to the Coordinating Center. The patient will then be removed from later reminders for visits and telephone contacts.

**Exhibit 7 - 1**

**CAPT Required Visits and Telephone Calls**

-----FOLLOW-UP MONTH-----

	IV		3	6	12	15*	18	24	30	36	42	48	54	60
<b>History</b>	X		X	X	X	X	T	X	T	X	T	X	T	X
<b>Refraction</b>	X			X	X			X		X		X		X
<b>Visual Acuity</b>	X		X+	X	X	X+		X		X		X		X
<b>Contrast</b>	X			X	X			X		X		X		X
<b>Reading</b>	X									X				X
<b>QOL Assessment</b>	X													X
<b>Ophthalmologic Exam</b>	X		X	X	X	X		X		X		X		X
<b>Color Stereo Photography</b>														
<b>Disc</b>	X													
<b>Macula</b>	X			X	X			X		X		X		X
<b>Fluorescein Angiography</b>	X				X			X		X		X		X
<b>Laser Treatment</b>	X				X*									

**LEGEND:**

- IV:** Denotes 'Initial Visit'
- X:** Denotes a procedure in a CAPT clinic
- T:** Denotes a telephone call
- \*:** Required only if 10 or more drusen remain at FV12
- +:** Visual acuity measurements at Safety Check visits do not need to have protocol refraction.

## CHAPTER 8

### EXAMINATION PROCEDURES

#### 8.1. VISUAL ACUITY EQUIPMENT AND FACILITIES

##### 8.1.1. Introduction

The visual acuity of CAPT patients will be measured following the procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) as adapted for the Age-Related Eye Disease Study (AREDS). The procedure is described in this section. The following equipment will be required: a set of three Lighthouse Distance Visual Acuity Test charts (second edition), which are modified ETDRS Charts 1, 2, and R, and a retro-illuminated box providing standardized chart illumination, as modified from the design by Ferris and Sperduto. The chart and boxes are manufactured by:

Lighthouse Low Vision Products  
36-02 Northern Boulevard  
Long Island, New York 11101  
Telephone: (718) 937-6959 or (810) 453-9923

Visual acuity testing is required at a distance of 3.2 meters and, for participants with sufficiently reduced vision, at 1 meter. The 3.2 meter distance should be marked clearly and permanently; the 1-meter distance must be measured, with a 1-meter stick, with the participant in a chair (Section 8.1.5).

##### 8.1.2. Visual acuity charts

Charts 1 and 2 are used for testing the right and left eye, respectively, and Chart R is used for refraction. The features of the charts are five high-contrast Sloan letters in each of 14 lines, lines of equal difficulty with respect to letter recognition, and a geometric progression of letter size (and, thus, an arithmetic progression of the logarithm of minimum angle of resolution [LogMar]) from line to line. The LogMar labeling of the lines corresponds to a testing distance of 4 meters and does not apply to testing at 3.2 meters. Charts 1, 2, and R have different letter sequences. Participants should be prevented from seeing Charts 1 and 2 until refraction has been completed and the visual acuity test begins.

##### 8.1.3. Visual acuity box

The dimensions of the light box are 24 and 3/4 inches by 25 inches and 3/4 inches by 7 inches. The box can be mounted on a wall or on a cylindrical stand manufactured by Lighthouse Low Vision Products. The stand is mounted on a five-pronged wheelbase, with each prong about 14 inches long; two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied. The rear of the box provides storage space for the two charts not being used.

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

#### 8.1.4. Illumination

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

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

- New tubes should be kept “on” for about 4 days (96 hours, does not have to be continuous), and
- All tubes should be replaced once a year. A sticker should be placed on the light box indicating the date of replacement along with the initials of the person who replaced the bulb. The Coordinating Center will remind each Clinical Center to replace tubes annually.

The fluorescent tubes should also be checked periodically for proper functioning. Replacement tubes can be purchased at a local store or from Lighthouse Low Vision Products. Keeping a back-up set of tubes that have been kept on for 96 hours is strongly advised.

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

#### 8.1.5. 3.2- and 1- meter visual acuity lanes

A distance of exactly 3.2 meters (10 feet and 6 inches) is required between the **participant’s eyes** and the visual acuity chart for the 3.2-meters test, and a distance of exactly 1-meter (39 and 3/8 inches) is required for the 1-meter test.

The room for visual acuity testing must have, in addition to the 3.2-meters lane, space for the visual acuity box (and possibly a stand) and space for the participant. Minimum room-length requirements vary according to how the box is mounted and whether the participant sits in a chair or stands for the 3.2-meters test.

- Wall-mounted box: In addition to the 3.2-meters lane, 7 inches must be allowed for the depth of the box plus space for the participant to sit or stand.



- Stand-mounted box: In addition to the 3.2-meters lane, 13 inches must be allowed for two of the stand's casters to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the participant to sit or stand.

## Marking the distance

### 3.2 meters

1. If the visual acuity box and the chair are permanently affixed, distance measurements generally do not need to be made for every patient to ensure the correct distance. However, measurements may need to be made if the patient sits forward in the chair due to obesity or a physical condition that keeps the patient leaning forward.
2. If the box is mounted on the wall but the participant's chair is not permanently affixed, the 3.2-meter distance of the participant's eye from the chart must be marked clearly and permanently.
3. If the box is mounted on a movable stand, the 3.2-meters distance must be marked clearly and permanently on the floor. The location and orientation of the box must be rechecked each time a new chart is put in place or the box is touched. When the stand touches the rear wall of the room, two of the five casters should touch the wall.

### 1 meter

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

## 8.2. REFRACTION TECHNIQUE

### 8.2.1. Introduction

The technique described below (See Chart 8-1) is required for CAPT participants whenever a manifest refraction and best-corrected visual acuity measurement is indicated by the study protocol. Any standard visual acuity chart, such as Refraction Chart R or a Projecto-Chart, and any test distance can be used for determining the best lens correction in each eye. This is permitted so that any refraction room at the Clinical Center can be used, minimizing waiting time for the participant. If the standardized test (3.2-meters, Chart R) is not used, however, an over-refraction with spheres should be done with Chart R at 3.2-meters prior to testing visual acuity (Section 8.2.7, Adjustment for non-standardized test conditions). Charts 1 and 2 are not used for refraction, only for visual acuity testing. The right eye is refracted first and then the left eye.

### 8.2.2. Beginning approximate refraction.

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

**For the Initial Visit**, the result of a subjective refraction on a previous visit can be used as the beginning approximate refraction for the CAPT initial visit. If this is not available, the procedures described below should be followed.

1. If the participant's visual acuity is 20/200 or better with the participant's present distance glasses, the glasses are measured with a lensometer and these measurements are used as the beginning approximate refraction.
2. If the participant's uncorrected visual acuity is 20/200 or better and the participant does not have glasses for distance vision, the beginning approximate refraction is no lens correction (plano). Acceptable alternatives are to perform retinoscopy or to use an automated refractor.
3. If the participant's visual acuity is less than 20/200 in either eye with the participant's present distance glasses (or without correction, if the participant does not have glasses), Retinoscopy should be performed by an examiner proficient in this procedure. An acceptable alternative is to conduct an arbitrary trial with any lenses to bring acuity to 20/200 or better; another is to use an automated refractor.

The lens correction obtained is used as the beginning approximate refraction for determining best-corrected visual acuity (Section 8.3).

**For Follow-up Visits**, the beginning approximate refraction from the previous CAPT visit, as written in the CAPT Record of Subjective Refraction, should be used for all follow-up visits.

### 8.2.3. Subjective refraction.

The trial frame is placed and adjusted on the participant's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. (It is permissible to use a phoropter for subjective refraction, using the -.25D lens to check the sphere instead of the -.37D lens. However, for testing visual acuity [Section 8.3], the lenses from the final phoropter refraction must be placed in a trial frame and the final sphere must be rechecked as described in Section 8.2.6, Refining final spherical power). The left eye is occluded and the beginning approximate refraction, as determined above, is placed in the right lens cells with the cylindrical correction anterior. If Chart R is used, it should be read at a distance of 3.2 meters. Other standard eye charts may be read at a distance of 10 to 20 feet directly or with a mirror. If visual acuity is too poor for the participant to see the largest letters on the chart at this distance, see Section 8.2.8 Refraction for a participant with poor visual acuity.

#### 8.2.4. Determination of spherical refraction.

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

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

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

Next, a -0.37 sphere is held in front of the trial frame and the participant is asked if the vision is “better,” “worse,” or “no different.” (If using a phoropter, which usually does not contain -.37D lenses, it is permissible to use a -.25D lens instead. Before testing visual acuity [Section 8.3], the lenses from the final phoropter refraction must be placed in a trial frame and the final sphere must be rechecked as described in Section 8.2.6, Refining final spherical power).

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

1. In certain situations, the participant is unable to read more letters, but is convinced that the vision is actually improved. If the examiner believes that this is the case, the additional minus lens can be added. At any stage in the examination, no more than 0.25 diopters of minus should be added without an increase in the number of letters read correctly. The additional minus lens should not be added if the participant reads fewer letters but states that acuity is better. There is a general attempt in this refraction protocol to avoid “over-minusing” the participants. However, when plus cylinders are in the refraction, one must be careful not to unnecessarily withhold minus which may

be necessary for the participant to accept the needed plus cylinders later in the refraction. Minus spherical power is added in - 0.25-diopter increments until the participant shows no further improvement in vision.

2. If the participant says the vision is “not different” or “worse” no minus power should be added and the spherical determinations are complete. If minus power has been added, a +0.50 sphere is tried again to determine if more plus will be accepted.

### 8.2.5. Determination of cylindrical refraction

For purposes of this discussion, only plus cylinder techniques are presented.

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

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

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

2. **Cylinder power determination.** A change in cylinder power is tested by adding the cross-cylinder, first with the positive axis and then with the negative axis coincident with the cylinder axis. For this test, the participant is requested to **focus attention on a round letter on the lowest line on the chart he or she is able to read**. If the participant prefers the positive axis coincident with the cylinder axis, the power of the correcting plus cylinder is increased by an additional +0.25 diopter. If the participant prefers the

negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. The process is repeated until the participant finds neither position definitely better than the other. As plus cylinder is added, the examiner should recognize that the spherical equivalent of the refraction is being changed. More minus spheres may be needed as plus cylinders are added. When using plus cylinders, for every 0.50 diopter of cylinder power added, the sphere should be changed by -0.25 diopter. If, at any time, the preference with the cross-cylinder indicates that cylinder power should be removed entirely, the 0.25 cylinder should be rotated 90 degrees from its original position. The axis should be refined and the power should be tested again.

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

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

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

In CAPT, minus cylinders may not be used.

### 8.2.6. Refining final spherical power.

When neither the power nor the axis of the cylinder can be improved, the power of the sphere is refined by testing with +0.25 sphere and -0.37 sphere and changing the spherical power by .25D, either plus or minus. If the sphere is changed at this point, the cylinder should be rechecked. This process is repeated until no further significant lens changes are made. The spherical refinement **must** be done using a trial frame, even if the refraction was done using a phoropter.

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

The lens corrections obtained in this way for the right eye are recorded on the CAPT data collection form and the CAPT Record of Subjective Refraction as the corrections obtained by subjective refraction for the right eye. The entire process is repeated for the left eye.

#### **8.2.7. Adjustment for non-standardized test conditions**

If a test distance other than 3.2 meters is used for refraction, the participant should be taken to the site of visual acuity testing. At this site, a final adjustment of the sphere (as outlined in Section 8.2.6, Refining final spherical power) should be made at 3.2 meters just before visual acuity testing, using Refraction Chart R with appropriate lighting. If this refraction differs from the initial refraction, this lens correction should be recorded on the data collection form. Similarly, if a Phoropter is used for the subjective refraction, a final check on the sphere (as described in Section 8.2.6) should be performed with a trial frame using the 3.2-meter refraction lane and Refraction Chart R. A change of spherical power in these circumstances does not require rechecking the cylinder power or axis.

#### **8.2.8. Refraction for a participant with poor visual acuity**

If it is not possible to perform a subjective refraction at 10 to 20 feet because visual acuity is too poor for the participant to see the largest letters on the refraction chart at this distance, the refraction should be attempted at 1 meter. If the subjective refraction can be performed successfully at 1 meter, a +0.50 sphere should be subtracted from the 1-meter refraction to make the correction appropriate for the 3.2-meter distance. The 3.2-meter correction should be entered on the data collection form in the space provided for distance subjective refraction. (NOTE: Visual acuity will be tested first at the 3.2-meter distance even if the participant cannot be refracted at this distance. If the number of letters read correctly at 3.2 meters is 15 or less, visual acuity must also be tested at 1 meter, in which case the +0.50 sphere should be added to the 3.2-meter refraction.)

### 8.3. TESTING BEST-CORRECTED VISUAL ACUITY

See Chart 8-2 for a summary of the CAPT visual acuity testing protocol.

#### 8.3.1. 3.2-meter test

TESTING OF ALL EYES BEGINS AT 3.2 METERS. First, the right eye is tested with Chart 1 and then the left eye is tested with Chart 2. Each chart should remain hidden from view until the eye in question is ready for testing.

The distance from the participant's eyes to the visual acuity chart must be exactly 3.2 meters (10 feet and 6 inches). The participant may stand or sit for the 3.2-meter visual acuity test. If the participant is seated, his or her back should fit firmly touching the back of the chair. The examiner should ensure that the participant is standing or sitting comfortably, that the head does not move forward or backward during the test, and that the participant's eyes remain at the 3.2-meter distance.

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

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

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

When the participant says he or she cannot read a letter, he or she should be encouraged to guess. If the participant identifies a letter as one of two or more letters, he or she should be asked to choose one letter and, if necessary, to guess even if the next letter has already been read. The examiner may suggest that the participant turn or shake his or her head in any manner if this improves visual acuity. If the participant does this, care must be

taken to ensure that the fellow eye remains covered. In some cases involving eccentric fixation, it may be necessary to occlude the fellow eye by inserting a tissue behind the trial frame. When it becomes evident that no further meaningful readings can be made (usually with the participant being unable to guess at a letter), despite urgings to read or guess, the examiner should stop the test for that eye.

There are several reasons for encouraging participants to guess: (1) Participants' statements that they cannot identify a letter are often unreliable; (2) encouraging them to guess helps to maximize the participant's effort; (3) it helps to assure uniformity among procedures performed in different clinics; and (4) it may help to prevent participant bias (malingering).

### 8.3.2. 1-meter test

Eyes reading 15 or fewer letters correctly at 3.2 meters should be tested at 1 meter. If the trial frame is to be removed when changing the test distance from 3.2 meters to 1 meter, the testing chart (Chart 1 or 2) should first be removed from view to prevent the participant from reading the chart with the fellow eye.

**Before testing at 1 meter, a +0.50 sphere should be added** to the 3.2-meter correction already in the trial frame to compensate for the closer testing distance. The participant may stand or sit for the 3.2-meter test, but must sit for the 1-meter test. (As indicated in Sections 8.1.5 and 8.2.3, the participant should be seated comfortably with his or her back firmly placed against the back of the chair.) The avoidance of any head movement forward or backward is particularly important during the 1-meter test. The participant should be asked to read only the first 5 lines at 1 meter.

After the test of the right eye is completed, occlude the left eye and replace Chart 1 with Chart 2. The test is repeated for the left eye, starting at 3.2 meters. When testing of the left eye is completed, Chart 2 should be removed from view; Chart R may be mounted in preparation for the next participant.

### 8.3.3. Scoring best-corrected visual acuity

The examiner records each letter identified correctly by circling the corresponding letter on the CAPT data collection form. Letters read incorrectly are marked with an "X" and letters for which no guesses are made are not marked on the form. Each letter read correctly is scored as one point.

### 8.3.4. Legal blindness

Assessing legal blindness (20/200 or worse) with the visual acuity charts used in this study may present a problem. On standard Snellen charts, the line below 20/200 is 20/100, and so the usual definition of legal blindness (20/200 or worse) could be reworded "worse than 20/100." The ETDRS charts, however, contain two lines of 20/160 and 20/125 between the 20/200 and 20/100 lines, and so a participant, who should be considered legally blind, may actually read better than 20/200 but worse than 20/100 when tested on the ETDRS charts.



This may prevent participants from being designated legally blind, depriving them of economic and social benefits. It is suggested that legal blindness be assessed with standard Snellen acuity charts.

#### 8.4. CONTRAST THRESHOLD TESTING

See Chart 8-3 for a summary of the CAPT contrast threshold testing protocol.

##### 8.4.1 Contrast Threshold Testing Equipment and Facilities

The contrast chart of Pelli and Robson is used for testing the contrast threshold of study eyes. The name of the distributor closest to each clinic can be requested from the distributor Clement Clarke, Inc., 3128-D East 17th Avenue, Columbus, Ohio 43219 (614) 478-2777. The chart should be hung on the wall during testing and kept out of sight at other times. Incident light falling on the chart should be between 75 and 125 foot-candles with no glare or shadows.

Refraction and visual acuity testing should precede contrast threshold testing.

##### 8.4.2. Testing Contrast Threshold

The right eye is tested first. The eye that is not undergoing the testing procedure should be occluded. Move the patient to 1.0 meter from where the chart will be located. Patients may sit or stand so that the level of their eyes is approximately in the center of the chart. **The lens power of the eye should be increased by +0.50 D from the refractive error determined at 3.2 meters.** Changing the spherical lens may be easier than adding another lens to the anterior compartment of the trial frame. Hang the chart so that the patient's eyes are aligned with the center of the chart.

Explain to the patient that the chart consists of same-sized letters in groups of three which go from high contrast to low. Tell the patient to guess once at each letter on the chart, beginning with the letter in the upper left-hand corner of the chart and reading across each row of two groups of three letters of equal contrast. As the patient reads each letter, circle each correct letter, put an "X" on each incorrect letter, and leave letters not attempted unmarked. Write the total number of letters correct in each set of three letters onto the corresponding answer space. Write "0" in the spaces corresponding to groups in which none of the letters were attempted. The patient should not be coached, but if he/she changes an incorrect response to a correct one before moving onto the next letter, the letter should be counted as correct. The patient must state one definitive answer per letter. Patients should be encouraged to guess even after they believe that the letters have disappeared. Patients may stop the test when they state that they cannot see anything in the next group of three letters, after being encouraged to guess.

## 8.5. READING TEST

See Chart 8-4 for a summary of the CAPT reading testing protocol.

### 8.5.1. Reading Test Equipment and Facilities

The MN Read charts are to be used for determining the critical print size, that is, the print size at which reading speed declines. The charts are available from Lighthouse Low Vision Products, 30-02 Northern Boulevard, Long Island City, NY 11101, (718) 937-6959 or (810) 453-9923. Charts are printed with 19 sentences of decreasing print size. The 19 sentences are divided between the front and the back of the card. Incident light falling on the chart should be between 75 and 125 foot candles with no glare.

Refraction, visual acuity and contrast threshold testing should precede the reading test.

### 8.5.2. Testing Reading

The reading test will be administered at the initial visit and at the 36-month and 60-month follow-up visits. The right eye will be tested first. The eye that is not undergoing the testing procedure should be occluded. Move the patient to the chair where the reading test will be performed and adjust the lighting if necessary. **The lens power for the eye should be increased +2.0 D from the refractive error determined at 3.2 meters.** Changing the spherical lens may be easier than adding another lens to the anterior compartment of the trial frame. Cover the text of the MN Read chart with a non-transparent cover sheet of paper and adjust the distance from the patient's eye to the center of the chart to 40 cm. A length of fishing line, which does not stretch, may be attached to the trial frame to aid in checking the distance both during setup and during the test.

Explain to the patient that you will be asking him/her to read single sentences of decreasing size. Instruct the patient to read aloud "as quickly and accurately as possible". The patient should not look at the text of each sentence until the examiner instructs him/her to start reading. With the data recording sheet in front of you and a pen at hand, instruct the patient to start reading the largest text by pulling down the cover sheet. Start the stopwatch as soon as you tell the patient to start, and stop it as soon as the last word has been read. Record the time to the nearest tenth of a second, record the number of words read incorrectly on the initial attempt, and reset the stopwatch to zero. Repeat the procedure for each sentence until the patient cannot read any words in a sentence. Patients should be encouraged to guess even when they believe the words are unreadable. Check the box marked "not attempted" for each sentence not read. If a technical error, (e.g. stopwatch malfunction) occurs during a sentence, resulting in no data or invalid data, the time should be coded as XX.X and errors as XX. The maximum time allowed per sentence is 99.9 seconds. The patient must attempt to read a sentence for a minimum of 30 seconds before you end the test.

## 8.6. BLOOD PRESSURE MEASUREMENT

Blood pressure measurements will be taken from the patient's arm by a CAPT certified examiner using an appropriate sphygmomanometer. Measurements from the patient's wrist or finger are not appropriate. Instructions for preparing the participant, using the proper techniques, utilizing equipment, and measuring and recording the blood pressure are provided below.

### 8.6.1. Participant Preparation

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

### 8.6.2. Technique

The following directions are generally for a sphygmomanometer requiring the use of a stethoscope. If using a digital readout blood pressure monitor, follow the manufacturer's instructions.

1. Use a standard sphygmomanometer to measure the blood pressure. It is important that the instrument be used correctly by a person skilled in its operation. The sphygmomanometer should be serviced at least annually to ensure continued accuracy. Place the lower edge of the cuff with its tubing connections approximately 1 inch above the natural crease of the inner aspect of the elbow (2.5 cm above antecubital space).
2. Wrap cuff snugly about arm with inflatable inner bladder centered over area of brachial artery (medial surface of arm).
3. Be sure that the connecting tube attached to the device is away from the participant's body and that the tube attached to the inflating bulb is close to the participant's body. Secure the wrapped cuff firmly by applying pressure on the locking fabric fastener over the area where it is applied to the cuff.
4. Attach the cuff connection and inflate the cuff while palpating the radial pulse and watching the column. Inflate the cuff until sufficient pressure is applied, at which point the pulse will no longer be felt. Deflate slowly at 2 mm per second until the pulse is felt again. Remember that number and immediately release all the pressure in the cuff.

5. Add 30 mmHg to the value at which the pulse was no longer felt. This value is the peak inflation level to which the cuff is to be inflated for all readings.

### 8.6.3. Stethoscope

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

### 8.6.4. Measuring the Blood Pressure

1. Place the earpieces of the stethoscope into your ears.
2. Apply the endpiece of the stethoscope over the brachial artery, just below, but not touching, the cuff or tubing.
3. By closing the bulb thumb valve and squeezing the bulb, inflate the cuff at a rapid but smooth, continuous rate to the peak inflation level previously determined (Section 8.6.2, Step 5). The examiner's eyes should be level with the mid-range of the manometer scale and focused at the peak inflation level.
4. By operating the thumb valve slightly and maintaining a constant rate of deflation at approximately 2 to 3 mmHg per second, allow the cuff to deflate. As the pressure falls, the Korotkoff sounds become audible over the artery below the cuff and pass through the four phases as the pressure declines and sounds disappear. The muffling and disappearance are sometimes referred to as the 4th and 5th "points."
5. The five phases of Korotkoff sounds are as follows:

Phase 1 - The period marked by the first appearance of faint, clear "tapping" sounds that gradually increase in intensity.

Phase 2 - The period during which a murmur or "swishing" quality is heard.

Phase 3 - The period during which sounds are crisper and increase in intensity.

Phase 4 - The period marked by the distinct, abrupt muffling of sounds so that a soft, "blowing" quality is heard.

Phase 5 - The point at which sounds disappear.

6. The systolic blood pressure is marked by the point at which the initial “tapping” sound is heard (Phase I). To make certain the sound is not extraneous, one should hear two consecutive beats as the pressure falls. When the palpatory systolic pressure is higher, it should be recorded and noted as systolic pressure.
7. “Muffling” occurs when the crisp Korotkoff sounds change (recognized by a sudden diminution or disappearance of sound). This is the fourth phase. The fifth phase, when sounds become inaudible, is regarded as the best index of diastolic blood pressure in adults; this phase will be used for measuring diastolic blood pressure in the CAPT. The accuracy of determining the fifth phase depends on the efficiency of the stethoscope and the auditory acuity of the examiner. In some individuals, particularly hypertensive patients, the usual sounds heard over the brachial artery when the cuff pressure is high, disappear as the pressure is reduced and then reappear at a lower level. This early, temporary disappearance of sound is called the “auscultatory gap” and occurs during the latter part of phase 1 and phase 2. Because this gap may cover a range of 40 mmHg, one can seriously underestimate the systolic pressure or overestimate the diastolic pressure, unless its presence is excluded by first palpating the radial pulse until it disappears as the cuff pressure is raised.
8. The examiner should listen throughout the entire range of deflation until 10 mmHg below the level of the diastolic reading.
9. When all sounds have disappeared, the cuff may be fully deflated by opening the thumb valve, and the stethoscope earpieces may be removed from the ears.

#### **8.6.4. Recording the Blood Pressure**

All readings should be made to the closest even digit. For example, if the reading is slightly above 82 mmHg, it should be recorded as 82 mmHg. Any reading (systolic or diastolic) that appears to fall exactly between markings should be read to the next marking immediately above.

Record both systolic and diastolic pressures.

## Chart 8-3

### CAPT Contrast Threshold Testing

#### 1. Setting up the patient

- The right eye will be tested first. The eye that is not undergoing the testing procedure should be occluded.
- Move the patient to 1.0 meter from where the chart will be located. Patients may sit or stand so that the level of their eyes is approximately in the center of the chart.
- The lens power of the eye should be increased by +0.50 D from the refractive error determined at 3.2 meters. Changing the spherical lens may be easier than adding another lens to the anterior compartment of the trial frame.
- Hang the chart so that the patient's eyes are aligned with the center of the chart.

#### 2. Instructing the patient

- Explain that the patient should guess once at each letter on the chart, beginning with the letter in the upper left hand corner of the chart and reading across each row of two groups of three letters of equal contrast.
- The patient should not be coached, but if he changes an incorrect response to a correct one before moving on to the next letter, the letter should be counted as correct.
- The patient must state one definitive answer per letter.
- Patients should be encouraged to guess even after they believe that the letters have disappeared.
- Patients may stop the test when they state that they cannot see anything in the next group of three letters, after being encouraged to guess.

#### 3. Scoring the test

- As the patient reads each letter, circle each correct letter, put an "X" on each incorrect letter, and leave letters not attempted unmarked. Write the total number of letters correct in each set of three letters onto the corresponding answer space. Write "0" in the spaces corresponding to groups in which none of the letters were attempted.

## Chart 8-4

### CAPT Reading Test

#### 1. Setting up the patient

- The right eye will be tested first. The eye that is not undergoing the testing procedure should be occluded.
- Move the patient to the chair where the reading test will be performed and adjust lighting if necessary.
- The lens power for the eye should be increased +2.0 D from the refractive error determined at 3.2 meters. Changing the spherical lens may be easier than adding another lens to the anterior compartment of the trial frame.
- Cover the text of the MN Read chart with a non-transparent cover sheet of paper and adjust the distance from the patients eye to the center of the chart to 40 cm. A length of fishing line, which does not stretch, may be attached to the trial frame to aid in checking the distance both during setup and during the test.

#### 2. Instructing the patient and scoring the test

- Explain to the patient that you will be asking him to read single sentences of decreasing size. Instruct the patient to read aloud "as quickly and accurately as possible". The patient should not look at the text of each sentence until the examiner instructs him to start reading.
- With the data recording sheet in front of you and a pen at hand, instruct the patient to start reading the largest text by pulling down the cover sheet. Start the stopwatch as soon as you tell the patient to start, and stop it as soon as the last word has been read. Record the time to the nearest tenth of a second, record the number of words read incorrectly on the initial attempt, and reset the stopwatch to zero. Put an X through any words read incorrectly to help keep track of errors.
- Repeat the procedure for each sentence until the patient cannot read any words in a sentence.
- Patients should be encouraged to guess even when they believe the words are unreadable. The patient must attempt to read a sentence for a minimum of 30 seconds before you stop the test. The maximum time allowed is 99.9 seconds per sentence.
- Check the box marked "not attempted" for each sentence not read.
- If a technical error (e.g. stopwatch malfunction) occurs during a sentence, code the time as XX.X and errors as XX.

## Chart 8 - 1

### CAPT Refraction Protocol

#### 1. Setting up the patient

The right eye will be refracted first. The eye that is not undergoing the testing procedure should be occluded.

- Determine the beginning approximate refraction and insert the lenses in the trial frame or Phoropter.
- Place Chart R or any other visual acuity chart 3.2 m from the patient.
- Ask the patient to read down the chart to determine the lowest line read well.

#### 2. Determination of spherical refraction

- Direct the patient to focus on the lowest line read well. Offer a +.50 D spherical lens and ask if the lens makes the image better, worse, or no different. Change the patient's lens power by +.50 D and repeat the process until the patient responds that the offered lens makes the image worse.
- Direct the patient to read the chart to determine if the lowest line read well has changed. Offer a -.37 spherical lens and ask if the lens make the image better worse or no different. If the patient responds that the image is better and can read at least one additional letter, change the patient's lens power by -.25 D and repeat the process until the patient responds that the offered lens makes the image worse or is no different.

#### 3. Determination of cylindrical refraction

- Direct the patient to focus on a round letter on the line above the lowest line read well. Offer the cross-cylinder with the positive axis  $45^\circ$  to one side and then  $45^\circ$  to the other side of the patient's cylinder axis. Ask which position the patient prefers or if the images are equally bad. Move the patient's axis  $5^\circ$  to  $15^\circ$  toward the preferred axis. Repeat the process until the patient responds that the two positions are equally bad.
- Direct the patient to focus on a round letter on the lowest line read well. Offer the cross cylinder first with the positive and then the negative axis coincident with the cylinder. Ask which position the patient prefers and change the patient's cylinder lens by .25 D in the direction of the preferred axis presentation. Repeat the process until the patient responds that the two positions are equally bad. For every .50 D change in cylindrical power, the spherical power should be changed by .25 D in the opposite direction as the change in cylindrical power.

#### 4. Refinement of spherical refraction

- Offer +.25 D and -.37 spheres and change power by .25 increments according to the rules in step 2 above. If the sphere changes, the cylinder axis and power should be rechecked using the rules in step 3 above
- Repeat the process in steps 2 to 4 above until there are no changes.



## Chart 8 - 2

### CAPT Visual Acuity Testing

#### 1. Setting up the patient

The right eye will be tested first. The eye that is not undergoing the testing procedure should be occluded.

- Testing of all eyes begins at 3.2 meters.
- The right eye is tested first using Chart 1.
- After the right eye is tested, the left eye is occluded and Chart 1 is replaced with Chart 2. The left eye is then tested.
- Eyes reading 15 or fewer letters correctly at 3.2 meters should be tested at 1 meter.
  - Before testing at 1 meter, a +0.50 sphere should be added to the 3.2-meter correction already in the trial frame.
  - The patient should be asked to read only the first 5 lines at the 1-meter distance.

#### 2. Instructing the patient

- Explain that the chart has letters only and no numbers.
- Instruct the patient to read slowly.
- If the patient says he cannot read a letter, he should be encouraged to guess.
- When it is apparent that no more letters can be read, after the patient is encouraged to guess, stop the test for that eye.

#### 3. Scoring the test

- Circle the letters read correctly, put an "X" on letters read incorrectly, and make no marks on letters not attempted. Each letter read correctly is scored as one point.
- If the patient changes a response before reading the next letter, the correction is accepted. If the patient changes the response after reading the next letter, the correction is not accepted.

## CHAPTER 9

### MEASUREMENT OF QUALITY OF LIFE (QOL)

#### 9.1. BACKGROUND AND RATIONALE FOR QUALITY OF LIFE ASSESSMENT

In the past decade, researchers have generally agreed that optimal health extends beyond traditional clinical markers and patient reported symptoms. "Quality of life" (QOL) is a term used for this broader conceptualization that is commonly viewed as including dimensions of physical, social, and role functioning (Mangione, 1993). It is also generally accepted that QOL is best measured in specific patient groups with both a condition specific measure and a general health status measure. The NEI-VFQ-25 has been designed specifically for use in populations subject to visual impairment; it has been field tested in populations that included patients with AMD. The NEI has mandated its use across all of its clinical trials. This common usage will provide a strong base for comparing the relative impact of the common forms of vision threatening disease (Kupfer, 1996).

Application of these assessments to the CAPT population will allow characterization of patients with bilateral drusen and will capture the impact of conversion to unilateral development of CNV (200 to 250 patients) and conversion to bilateral development of CNV (60 patients). These data will be important in economic analyses of prophylactic laser treatment as well as any preventive therapy for advanced AMD. No direct data on the impact of treatment on quality of life can be obtained from CAPT since each patient has one eye assigned to treatment and one eye assigned to observation.

#### 9.2. MODE OF ADMINSTRATING THE QOL QUESTIONNAIRE

The questionnaire will be administered at the Initial Visit and at the 60 Month Visit. The primary mode of administration will be self-administration. At baseline, all patients will have visual acuity of 20/40 or better in each eye and will face no vision obstacles to self-administration. Over the follow-up period, some patients will develop complications and lose vision; however, only 6% of patients (60) are expected to have bilateral involvement from CNV. These patients, and patients who develop physical impairments, may find self-administration of the tests difficult. Clinic Coordinators will identify patients with decreased vision and/or physical impairments and ask them if they anticipate difficulty in completing the form. If the patients respond positively, the Clinic Coordinator will ask the patient if she/he would agree to receive a telephone call from a trained interviewer from the CAPT Coordinating Center to set up a time for administration of the questionnaire over the telephone.

The Research Associate will call patients who agree to the telephone administration. She will set up a convenient time for the interview and call at the appointed time to administer the questionnaires. The patient's name will be kept in a confidential manner by the Research Associate and will not appear on any data collection forms.

### 9.3. METHODS FOR ADMINISTRATION OF THE QOL QUESTIONNAIRE

The NEI VFQ-25 questionnaire will be separate from the data collection forms completed by CAPT clinic staff. The self-administered questionnaire will follow the format of the published version and will be printed using a large point size to allow readability by those with modest deficits in visual acuity. Clinic Coordinators will provide the patient with the questionnaire and a brief set of instructions. The Clinic Coordinator will review the instructions with the patient and answer any questions that the patient might have about how to complete the form. Once the patient has completed the form, the Clinic Coordinator will immediately review the form to make sure that all questions have been answered and that the responses are legible. If any problems are identified, the Clinic Coordinator will request that missing or illegible responses be revised by the patient. Completed forms will be sent to the Coordinating Center with other data collection forms completed for the visit.

The Research Associate at the Coordinating Center will be responsible for administering the questionnaire over the telephone. Prior to administering the questionnaire to CAPT patients, the Research Associate will have been instructed in the proper technique for asking the patient questions and for responding to questions and comments by the patient.

## CHAPTER 10

### CLINICAL CENTER MANAGEMENT

#### 10.1. INTRODUCTION

Each Clinical Center in the Complications of AMD Prevention Trial (CAPT) is directed by the local CAPT Principal Investigator, who must be a certified CAPT Participating Ophthalmologist. Each clinical center must have one or more people who fill the following roles:

- Participating Ophthalmologist: Responsible for enrolling, treating, and following CAPT patients;
- Clinic Coordinator: Responsible for supervising activities related to CAPT and integrating these with clinic operations;
- Visual Function Examiner: Responsible for performing masked examinations of visual acuity, contrast threshold, and reading;
- Photographer: Responsible for performing color stereo photography and fluorescein angiography as specified by the protocol.

Some Principal Investigators may choose to have more than one clinical site for CAPT operations in order to enhance enrollment and follow-up performance. Each site must be fully certified with respect to having the required space, equipment, resource materials, and staffing. Staffing may be shared across sites within a clinical center; however, a full CAPT team (Principal Investigator, Clinic Coordinator, Visual Function Examiner, and Photographer) must be available at each site during CAPT patient visits.

During follow-up, the Visual Function Examiner must be masked to the treatment status of each eye. Therefore, during follow-up, the same person may not serve as the Clinic Coordinator and Visual Function Examiner to a patient. However, if necessary, the same person may serve both roles at the initial visit before treatment assignment.

#### 10.2. RESPONSIBILITIES OF CLINICAL CENTERS

The responsibilities of the CAPT Clinical Center team include the following:

- To assess eligibility of patients for the Complications of AMD Prevention Trial.
- To enroll eligible patients.
- To perform laser treatment to each eye assigned to treatment according to the CAPT treatment protocol.
- To manage each patient in accord with the randomized assignment provided by the Coordinating Center and the instructions in the CAPT Manual of Procedures.

- To arrange for each patient enrolled in CAPT to be examined in the CAPT clinic according to the schedule established.
- To complete the proper data collection forms and obtain the other materials required at each scheduled clinic examination or telephone contact.
- To transmit all forms, documents, and materials to the Coordinating Center and Reading Center as expeditiously as possible after each clinic visit.
- To respond promptly to requests from the Coordinating Center and Reading Center.
- To maintain CAPT patient records in an easily accessible but confidential manner.
- To maintain up-to-date informed consent documents that meet CAPT standards and the standards of the local institutional review board.
- To maintain all equipment and supplies required for CAPT
- To assure that all CAPT staff are trained and certified as required.
- To provide representation (Principal Investigator and Clinic Coordinator) at all meetings of the CAPT Research Group.
- To cooperate in scheduling and conduct of the clinic monitoring visits.

### **10.3. CLINIC COORDINATOR**

#### **10.3.1. Qualifications**

Because day-to-day responsibility for most clinical center tasks, apart from vision testing, usually falls to the Clinic Coordinator, it is important that this individual be selected carefully, thoroughly trained in the CAPT protocol, and recognized as the local CAPT "expert" in the clinical center. It is essential that the center Principal Investigator and the local institutional administration recognize the Clinic Coordinator as a collaborating member of the CAPT research team and that sufficient time is allocated to the myriad of activities required. The coordination of CAPT should be the highest priority of the Clinic Coordinator.

The Clinic Coordinator has extensive contact with CAPT patients; therefore it is important that this individual have the ability to deal well with people. The rapport that frequently develops between a patient and the Clinic Coordinator is extremely important to assuring the continued cooperation of a patient throughout the course of a study, particularly when follow-up examinations are widely spaced temporally as in CAPT. Patients frequently turn to the Clinic Coordinator for clarification or confirmation of their discussions with the ophthalmologist or other physicians; therefore, it is mandatory that the Clinic Coordinator be a mature, responsible person with a thorough understanding of the CAPT protocol, design, and rationale. In addition, the Clinic Coordinator must have excellent organizational skills and attention to detail.

### 10.3.2. Responsibilities

The responsibilities of the Clinic Coordinator include, but are not limited to, the following:

- To coordinate clinical center site activities related to the CAPT
- To have a thorough understanding of the CAPT design and methods.
- To schedule and coordinate patient examinations.
- To arrange patient transportation, as necessary.
- To maintain patient interest in the study through scheduled contacts between clinic examinations and by demonstrating concern for patients' welfare and problems.
- To maintain complete and current residency and employment information on each patient enrolled for the duration of the CAPT.
- To provide a resource for other clinic personnel concerning the details of the protocol and decisions requiring notification of or approval from the Executive Committee.
- To provide the primary interface between the clinical center site and the Coordinating and Reading Centers by being the primary recipient of incoming mail from the US Postal Service, express carriers such as Federal Express, FAX communications, voice mail, and e-mail.
- To distribute materials and information to the appropriate CAPT team members.
- To coordinate use of CAPT patient education and recruitment materials, including slides, brochures, and exhibits provided by the Coordinating Center.
- To maintain required Study documentation, including:
  - ▶ Up-to-date *CAPT Manual of Procedures*, as provided by the Coordinating Center, with addenda in the form of protocol memoranda.
  - ▶ Scheduling notebook with the CAPT follow-up schedule for each patient.
  - ▶ Patient Log Book, containing CAPT identifiers (CAPT name code and number), patient name, enrollment date and treatment assignment as well as the signed consent form and the patient information sheet of each patient in CAPT identification number order.
  - ▶ Current addresses and other information required to contact each patient.
  - ▶ Log of all photographs sent to the Photograph Reading Center.
- To review all forms and materials for completeness and accuracy before they are sent to the Coordinating Center or Photograph Reading Center.
- To retain copies of all study forms sent to the Coordinating Center or Photograph Reading Center and records of corrections made to any forms, organized so as to be easily retrievable. Two sets of patient charts are recommended, one composed of CAPT forms maintained by the Clinic Coordinator and the other in the usual way for the clinical center.

- To promptly respond to edit queries and notices from the Coordinating Center and Photograph Reading Center regarding information or documents provided for CAPT patients.
- To remind each patient before each vision examination not to tell the Vision Examiner which eye was treated.
- To notify the Coordinating Center of any patient requiring administration of the quality of life instruments by telephone.
- To coordinate local arrangements for clinic monitoring visits so that all CAPT-certified personnel are available.
- To maintain a supply of current versions of all CAPT forms and to reorder supplies from the Coordinating Center as needed.
- To label materials or, in some cases, to verify labels placed by other CAPT personnel on materials, to be sent to the Photograph Reading Center and take responsibility for sending materials out.
- To notify the Coordinating Center concerning personnel changes that affect local CAPT operations.
- To communicate with the Coordinating Center concerning problems with maintaining data quality at the clinical center.
- To maintain the clinic organization as a well-coordinated unit for evaluating, treating, and following CAPT patients.
- To organize regular clinic staff meetings of all CAPT personnel.
- To inform the clinical center Principal Investigator of any problems with clinic management and to suggest ways to resolve them.
- To attend scheduled meetings of the CAPT Research Group.
- To assist clinic personnel with CAPT certification.
- To assure that the ophthalmologist spends sufficient time with each CAPT patient during follow-up examinations at the clinical center to satisfy the patient and to reassure the patient of the importance of continuing examinations and contact.
- To ensure that all budgetary items required for subcontracting are prepared and submitted in an accurate and timely manner.

### **10.3.3. Internal Communication**

The Clinic Coordinator should make certain that each person certified for the CAPT understands the role of the Clinic Coordinator. Telephone numbers and work schedules should be exchanged.

The Clinic Coordinator should explore benefit programs for patients within the local institution and learn how to facilitate patient participation in these programs. These may include reduced parking charges, low cost meals, reduced room rates at local hotels, special discounts on airfares, special arrangements for local transportation, etc. Clinic Coordinators from other studies are useful contacts for learning about local resources.

The Clinic Coordinator should arrange with the clinical center's Principal Investigator to meet regularly and to organize time for CAPT staff meetings particularly during the clinic start-up and patient enrollment phases. The Clinic Coordinator should establish in advance the best meeting time for all CAPT staff. The Clinic Coordinator should meet with business office or billing office staff to verify patient charges and to confirm which ones are to be charged to the CAPT grant. Procedures for third-party reimbursement should be reviewed.

#### **10.3.4. Interaction with Coordinating Center**

The Coordinating Center staff works closely with the Clinic Coordinator to resolve any problems that arise at CAPT clinical centers. The Coordinating Center staff has primary responsibility for training candidates for certification as CAPT Clinic Coordinators.

The Coordinating Center staff provides the following materials to the Clinic Coordinator:

- A copy of the *CAPT Manual of Procedures* and revisions as they become available.
- A copy of the *CAPT Forms Book*, which includes copies of all forms used in the CAPT, whether for data collection, clinic management, or study management.
- A patient log for assigning CAPT identification numbers and recording treatment allocations.
- A copy of the *CAPT Address Registry* that includes the name, address, telephone numbers, FAX, and e-mail address of personnel in all CAPT clinical centers and members of CAPT committees.
- Recruitment aids, such as copies of CAPT informational brochures for patients and referring ophthalmologists and slides for presentations at professional meetings.
- Other clinic and patient management aids, such as individual patient follow-up schedules, visit reminders, and printed labels for photographs.

The Clinic Coordinator should set up two special loose-leaf binders at the beginning of the CAPT, one for the individual follow-up schedules (Follow-up Notebook), and one for the Log Book. (The *Manual of Procedures*, *Address Registry*, and *Forms Book* are supplied in their own three-ring binders.) The Log Book is a permanent record containing the original signed consent forms and a copy of the patient contact information for each patient, in addition to all of the log sheets. A duplicate of the Log Book should be kept in another location, preferably in another building or at home. *The duplicate Log Book should be updated each time a new patient is entered into the CAPT and should be reviewed for completeness at least weekly during the recruitment period.*



Follow-up schedules are filed in patient ID order in the Follow-up Notebook. A copy of the follow-up schedule also is made for the patient's CAPT file. Study forms are provided on request by the Coordinating Center after the initial supply is depleted.

Whenever CAPT forms have been revised, the Clinic Coordinator is responsible for seeing that all old versions in the clinical center are destroyed so that they are not used by mistake. Under no circumstances should outdated forms be used. The Clinic Coordinator is responsible for explaining to other clinic staff any changes in procedures that are required by form revisions. He/she should consult personnel at the Coordinating Center whenever uncertain about such changes.

To supplement information in the Manual of Procedures and to communicate new procedures and policy expeditiously between updates to the Manual, numbered CAPT protocol memoranda are sent from the Coordinating Center or Photograph Reading Center. One copy of each memorandum should be filed in numeric order in a binder or file folder set up specifically for this purpose. A second copy should be inserted in the Manual of Procedures with the appropriate chapter and retained until the information is incorporated into the next revision of the chapter. Additional copies are made for any CAPT staff member who is affected by the new or revised information.

### **10.3.7. Interaction with Reading Center**

The staff of the Reading Center is available to resolve problems that arise regarding eligibility judgments based on review of pre-enrollment photographs, certification of Participating Ophthalmologists and photographers, as well as problems with photographic materials. Only original photographs should be sent to the Reading Center; copies should be made for the clinical center files. If during the course of the study an additional copy of a fluorescein angiogram is needed, a copy can be requested from the Reading Center Coordinator, at the clinic's expense.

### **10.3.8. Workspace**

With so many responsibilities, it is important that the Clinic Coordinator have adequate workspace. Private office space is necessary for obtaining patient histories, talking with patients and family members, making telephone calls to patients and physicians, and labeling photographs. The room should be large enough for the Clinic Coordinator's desk, file space for CAPT records and patient charts, and seating for the patient and family member(s). The doorway and floor space should accommodate a wheelchair. Ideally, the office should be near the CAPT Principal Investigator's office or primary examination room.

## **10.4. SCHEDULING AND COORDINATION OF PATIENT EXAMINATIONS AND DATA COLLECTION**

In most clinical centers, the Clinic Coordinator plays a major role during data recording, both by questioning and examining the patient directly regarding interim history, and, in some cases, by recording responses dictated by the ophthalmologist while examining the patient. Although the CAPT Clinic Coordinator is not responsible for testing vision and for recording the results of these examinations, this individual should check all such recorded information for completeness and consistency and verify the examiner. Therefore, it is important that the Clinic Coordinator have a thorough understanding of the procedures that take place for each required examination, the sequence in which these are best performed in the clinical center, the contents of the data collection forms and other forms to be completed, and local conventions that must be followed to maintain the clinical chart for each patient.

### **10.4.1. Initial Visit Examinations**

As long as patients are being enrolled in the CAPT, a complete Initial Visit evaluation is completed for every patient whom the ophthalmologist is fairly certain will meet the eligibility criteria for CAPT. Previous photographs or patient chart notes may be used to identify patients who are likely to be eligible. The medical history interview, which includes questions on the CAPT Initial Visit Form, may be done before or after the vision examination. A protocol refraction and vision examination are performed and the results are recorded on the appropriate component of the Initial Visit Form. This is the only visit for which the Clinic Coordinator may perform the refraction and vision examination if the Clinic Coordinator has also been certified as a Visual Function Examiner. Next, the normal clinical examinations and procedures are done. A CAPT-certified retinal specialist performs the clinical examination. If the patient is still considered eligible, enrollment into CAPT should be offered and signed written consent obtained before photography and angiography.

The Clinic Coordinator and the CAPT Ophthalmologist share responsibility for the patient's orientation into the CAPT, but the ophthalmologist must take responsibility for the initial discussion with the patient and family. The Clinic Coordinator should be present for the discussion and should make every effort to assure that all of the patient's questions and those of the family are answered satisfactorily. The patient is asked to sign the consent form after having had the opportunity to read it and ask questions. Fluorescein angiography and color photography may then be performed and administration of the quality of life instruments can be administered. After the fluorescein angiogram has been interpreted by the ophthalmologist, an assessment of eligibility should be performed by completing the CAPT Eligibility Checklist. The Clinic Coordinator checks that all items have been answered, signs and dates the form, faxes the Eligibility Checklist to the Coordinating Center, and calls to make arrangements for obtaining a randomized treatment assignment.

### **10.4.2. Randomization**

The patient must understand the concept of randomization in clinical trials. The Clinic Coordinator and Participating Ophthalmologist telephone the Coordinating Center, while the patient is in the clinical center, to obtain the random assignment by telephone. After a verbal review of the ophthalmologic eligibility criteria by the Participating Ophthalmologist and a Coordinating Center staff member, the CAPT ophthalmologist is told the assignment and asked repeat it to the person at the Coordinating Center. The Ophthalmologist should tell the Clinic Coordinator the eye to be treated and the Clinic Coordinator should also repeat the assignment to the person at the Coordinating Center. The ophthalmologist should treat the patient immediately. A request for randomization should not be made unless the patient is present and available in the same location as the laser used for treatment.

The Coordinating Center sends the Clinic Coordinator via facsimile a written confirmation of the treatment assignment and then mails the patient's individual follow-up schedule. The Initial Visit materials are sent to the Coordinating Center and copies are filed in the patient's CAPT chart, together with the treatment assignment confirmation and the follow-up schedule. An additional copy of the follow-up schedule should be placed in the Follow-up Notebook.

If the patient is not ready to sign the consent form during the Initial Visit, the patient may go home to think about enrolling in the trial. All parts of the Initial Visit must be completed within 28 days of randomization and treatment. Ideally the entire visit, randomization, and treatment will be performed on the same day. If a patient refuses to consider participation in the CAPT or if a patient is found to be ineligible, no materials are sent to the CAPT Coordinating Center or Photograph Reading Center.

### **10.4.3. Follow-up Visits and Schedule**

It is extremely important that both the Clinic Coordinator and the patient adhere to the follow-up schedule. The patient's Follow-up Schedule should be consulted whenever the patient is given an appointment for a follow-up examination. It is especially important to refer to the Schedule when an examination date is changed.

Each examination should be scheduled as close as possible to the target date. However, the procedure does allow time for rescheduling within the permissible time limits, thereby decreasing the number of missed examinations and calls. Whenever an examination is completed near the end of a time window, an attempt should be made to get back on schedule. The actual date of each examination should be written on the Follow-up Schedule in the appropriate place. Examinations not completed within the specified time limits are classified as missed.

#### **10.4.4. Follow-up of Patients Unable to Return for Scheduled Examinations**

Because of poor health or for other reasons, some patients may not be able to return to the clinical center for scheduled examinations despite their original intentions to do so. The general health status of the patient can be obtained by the Clinic Coordinator through telephone calls or visits to patients' homes. If the Clinic Coordinator discovers that the patient has died, the Clinic Coordinator should complete a Patient Death Form and submit it to the Coordinating Center. If the patient cannot be examined in the CAPT clinical center, a visit with a non-CAPT ophthalmologist or a home visual acuity examination should be attempted. A CAPT Visual Function Examiner may conduct the home examination. If the patient cannot be located through family members or friends, a Patient Search Form should be initiated.

##### **10.4.4.1. Outside Visits and Home Visits**

The patient's local ophthalmologist or optometrist may be asked to provide visual acuity information and photographs. Written documentation regarding the patient's visual acuity measurements should be obtained from the ophthalmologist who is currently following the patient. If this is not feasible, the Clinic Coordinator may accept the information provided by the ophthalmologist via telephone and document the call. Patients must sign a medical release form to authorize release of the information. A CAPT Outside Visit form should be completed and sent to the Coordinating Center.

Patients with special problems that preclude being seen in a clinic office for a scheduled CAPT examination may be visited at home. Examination of these patients by CAPT-certified staff at home or in an alternate location should mimic the clinic examination procedures as much as possible. A lens set and trial frames, a backlit visual acuity chart to be used for refraction, two additional CAPT visual acuity charts to measure visual acuity, and a tape measure or yardstick must be carried with the Vision Examiner. Supplementary lighting should be taken to the patient's home if the backlit CAPT chart's housing cannot be transported. Although the lighting level in the certified visual acuity lane is unlikely to be reproduced in the patient's home, the ambient lighting should be as bright as possible.

##### **10.4.4.2. Missed Examinations**

Special procedures have been developed for reporting contacts between patients who miss examinations and their non-CAPT ophthalmologists or optometrists. Whenever it is not possible to examine the patient in a CAPT clinical center or at home, the following procedures should be followed to provide as much useful information as possible.

- If a Study patient cannot complete a scheduled Study examination within the time window for that visit, the Coordinating Center should be notified by transmittal of a Missed Visit Form within two weeks of the close of the examination window.
- The patient should be contacted by telephone to schedule the next examination or to confirm the appointment for the next examination.

- The patient should be asked whether an eye examination has been completed during the time period covered. If so, the name of the ophthalmologist or optometrist, the address, and telephone number, if possible, should be obtained from the patient.
- The patient must be asked to sign a medical record release form allowing the outside ophthalmologist to provide information on the patient.
- The examining ophthalmologist or optometrist should be contacted and requested to provide the visual acuity measurements for both eyes. If fundus photographs and/or a fluorescein angiogram were taken at the time of the examination, a copy should be requested.

#### **10.4.4.3. Maintaining Contact**

Any time a patient misses a scheduled examination, the clinic coordinator should contact the patient immediately and arrange another appointment. If the patient cannot be located, an intensive search should be instituted immediately by the Clinic Coordinator. The Clinic Coordinator should use all available resources to locate the patient, including writing or telephoning each contact provided by the patient at time of enrollment or added since then. Because this search may be long and time-consuming, it is important that it be started as soon as any member of the clinic staff is aware that there is a problem. The steps taken to locate the patient should be documented on a Patient Search Form. In extreme cases when the clinic staff has exhausted all avenues and the patient has not been located the Coordinating Center should be notified.

### **10.5. CHECKING COMPLETED FORMS**

Before being transmitted to the Coordinating Center each data form should be carefully checked by the Clinic Coordinator. This process is extremely important because correcting errors that have entered the computerized data system is far more time-consuming and expensive than taking the appropriate steps to prevent errors. Every response on the forms should be checked for completeness, consistency with other information reported for the patient, and legibility. In addition, the person performing each procedure should sign the appropriate component.

#### **10.5.1. Completeness**

Each data form should be checked to assure that all pages of all components are included and in the correct order. Whenever any required item is unanswered or has a question mark for an answer, an edit query is generated at the Coordinating Center and transmitted to the Clinic Coordinator. Whenever there is doubt about how an item is to be answered, the Project Director or another member of the Coordinating Center staff should be contacted by telephone. Items for which an answer always is required usually appear on the left-hand side of each page of each form.

### **10.5.2. Consistency**

Questions that should be answered only for certain patients appear in boxes in the right hand column of each page of each form. An arrow leading from a specific answer to a box indicates that whenever that answer is checked, the additional information in the box also is required. Otherwise, items in the box should be left unanswered. Dates should be checked for accuracy. In particular, the date of an examination recorded on a data form should be the actual date the patient was examined and not the date when the data form is sent. Dates are edited at the Coordinating Center for consistency.

### **10.5.3. Legibility**

Write-in responses should be printed or typed so that they are clearly legible. Check marks, circles, and X's should be placed precisely so that there is no possibility of confusion regarding the response intended.

### **10.5.4. Photographic Materials**

Before photographic materials are sent to the Photograph Reading Center, each slide mount and fluorescein label should be carefully checked by the clinic coordinator for completeness and accuracy. Although printed labels are provided to the centers by the Coordinating Center, care must be taken that all write-in information is recorded correctly. Detailed instructions have been provided in Chapter 15. Clinic Coordinators or photographers are encouraged to contact the Photograph Reading Center staff with any questions regarding the labeling or preparation of the photographic materials.

## **10.6. EDITS AND CORRECTIONS**

### **10.6.1. Edit Queries**

The information recorded on the CAPT data forms is keyed by the Data Assistants in the Coordinating Center and then edited for anomalies by means of special computer programs. When there is a question regarding the answer to one or more of the items on a component, an edit query is issued to the Clinic Coordinator. The edit query gives CAPT identifying information about the patient, visit, and form component in question, and lists the item number(s) and the original answer ("old value") reported on the form. An explanation of the nature of the problem follows the list of items. When an edit query is received, the Clinic Coordinator should retrieve the patient's record from the files and determine the correct answer for each item listed. The Clinic Coordinator may need to consult with the physicians or other technical staff for specific medical information. Whenever a correction to the earlier value is required, the Clinic Coordinator writes in the new answer on the edit query, corrects the earlier response on the copy of the original data collection form by striking through it (so that it is still legible), writes the correct response, initials and dates the corrected item(s), sends the edit query back to the Coordinating Center, and attaches a copy of the edit query to the copy of the original form. The original response should not be obliterated either with white-out, marker, or by scratching through it.

### **10.6.2. Errors Discovered in Other Ways**

On occasion, clinic personnel may discover errors on forms in addition to those detected by the computer edit. When this occurs, an Error Correction Form should be completed and sent to the Coordinating Center, a copy attached to the copy of the original form; and correction of the response on the copy of the original form as described above.

### **10.7. ASSURING COMPLETENESS OF PATIENT FOLLOW-UP**

One of the most important duties of the Clinic Coordinator is maintaining good rapport with all CAPT patients and assuring that each patient's whereabouts are known at all times. Thus, it is essential that all requested information at the Initial Visit be recorded in full and updated regularly. Patients who die before follow-up in the CAPT is completed are reported to the Coordinating Center as soon as the Clinic Coordinator learns of the death. A Patient Death Report is submitted immediately.

### **10.8. PREPARING FOR FOLLOW-UP EXAMINATIONS AND TELEPHONE CALLS**

The following tasks should be performed before the patient appears for a scheduled follow-up examination or before telephone contact is initiated.

- Remind the patient of the scheduled appointment by telephone or mail in advance of the date.
- Ask the patient not to wear contact lenses to the appointment;
- Retrieve the patient's CAPT file.
- Label each page of the follow-up examination form with the labels containing the patient's name code, CAPT identification number, and visit code.
- Check that the Record of Subjective Refraction is complete and attach it to the pages of the data form to be completed by the Visual Function Examiner. (The Visual Function Examiner should have access to the refraction record but should not be able to refer to the vision measurements from the previous examination or to the treatment assignment.)
- Schedule appointments for photography as necessary.
- Be sure that any pertinent information received since the last examination is available to the ophthalmologist. This information may include photographs, fluorescein angiograms, etc.
- Put the Patient Information Form in the folder as a reminder to review and update the information.

## 10.9. UPDATING THE PATIENT'S CAPT FILE

The following things should be done to keep the patient's CAPT file as complete and up-to-date as possible at all times:

- The personal information on the patient, such as telephone numbers, place of employment, persons who can be contacted about the patient's whereabouts, etc., should be reviewed and updated at each examination and telephone call. Contacts already listed should be confirmed. If any changes are made, the information should be added to the Patient Information Form and duplicate Log Book.
- Be sure that copies of the forms, photographs, and all other information sent to the Coordinating Center and Photograph Reading Center are in the patient's file.

## 10.10. QUALITY ASSURANCE RESPONSIBILITIES

The validity and credibility of the CAPT depends to a large degree on the collection and reporting of high quality, accurate data. Each CAPT staff member should be aware of his/her responsibility for following the protocol, reporting data accurately and promptly, and resolving any problems that occur in CAPT-related activities. Although the local CAPT Principal Investigator bears primary responsibility for the accuracy and integrity of study data, much of the responsibility falls to the Clinic Coordinator.

In addition to the routine procedures described in previous sections, the primary quality assurance mechanisms to be implemented by the clinical center are:

- The person completing each examination and taking responsibility for the examination must be listed by name and certification number at the end of the section recording the data from the examination.
- Hard-copy documentation of all testing, procedures, and telephone calls should be obtained and kept in patients' CAPT files.
- Any errors or discrepancies discovered at the clinical center are corrected, regardless of the time elapsed since the data were collected, and reported to the Coordinating Center.
- Systematic data collection or reporting problems are brought to the attention of the responsible individual, CAPT Principal Investigator, and the Coordinating Center for review and resolution.

### 10.10.1. Guidelines for Documentation of CAPT Activities

In accordance with good research practice, it is essential that all CAPT patient-related activities be documented so that information in the clinical centers can be compared with the data in the CAPT database by CAPT site visitors and/or outside auditors as necessary. *Documentation should be complete for all patients enrolled in CAPT whether or not the patient was judged eligible after enrollment.*



Information should be included that documents:

- The eligibility status of each patient.
- That all reported procedures and tests were conducted according to protocol.
- That all procedures and examinations were performed by the reported personnel at the times reported.
- That the reported treatments were administered per protocol by the specified personnel or that protocol deviations have been reported.

In addition to CAPT-related forms, other clinical information is valuable for providing complete documentation of study-related procedures. The following section specifies the types of documentation that are recommended.

#### **10.10.2. Information To Be Included in the Medical Chart**

- Examination notes, dated and signed by the individual(s) performing the examination, and completed at the time of the examination.
- Copies of photography reports or logs.
- Copies of all internal or external patient-related correspondence.
- Signed and dated notes from telephone calls and other contacts with patients, their families, friends and physicians.
- Signed notes documenting patient education, counseling, and enrollment decisions regarding the CAPT.

Patient names and other identifiers should be retained on all such documentation so that the identity of the patient and the correspondence of examination results to the reported data may be confirmed. This information need not be retained in the CAPT files but may be kept in separate clinic files for each patient. The structure of these files may vary depending on local guidelines or requirements. However, some Clinic Coordinators find it expeditious to attach copies of all documents from which data were abstracted to the corresponding forms in the CAPT charts.

## CHAPTER 11

### CERTIFICATION PROCEDURES

#### 11.1 OVERVIEW OF CERTIFICATION PROCEDURES

It is important that all procedures in CAPT be standardized and that all individuals who are part of the CAPT Investigative Group understand the protocol to the degree necessary for them to fulfill their responsibilities. Clinic facilities must also meet specific standards in order to follow the CAPT protocol.

There are specific roles in the clinical centers that must be filled with certified personnel. These roles are Principal Investigator, Participating Ophthalmologist, Clinic Coordinator, Visual Function Examiner, and Photographer. Also, all personnel in the Coordinating Center, Reading Center, and Chairman's Office must fulfill certain criteria.

#### 11.2. CERTIFICATION CRITERION FOR ALL MEMBERS OF THE INVESTIGATIVE GROUP

Everyone engaged in CAPT must have a base amount of knowledge about CAPT so that questions from patients and others may be answered accurately. All members of the Investigative Group must complete a general knowledge assessment form about CAPT that requires knowledge of such basic facts as the name of the study, the definition of and implications of high risk drusen, the impact of the development of the advanced forms of age-related macular degeneration on vision, and the primary outcome measure. In addition, individuals are required to complete role-specific section assessments, as described below.

Knowledge assessment forms must be completed by the original CAPT group and by all new personnel at the time of hiring. The Project Director and Research Associate are responsible for reviewing the forms submitted by clinic coordinators and visual function examiners, respectively, and contacting the respondent if there are areas of misunderstanding. The Director of the CAPT Reading Center is responsible for reviewing the forms and materials submitted by ophthalmologists and photographers. The Project Director and Research Associate maintain a log of all people who have successfully completed the assessment.

#### 11.3. CERTIFICATION OF OPHTHALMOLOGISTS

All CAPT Participating Ophthalmologists are required to have completed a retinal fellowship or have equivalent experience. Participating Ophthalmologists must have specific knowledge of the major eligibility criteria, treatment protocol, and procedures for managing patients during follow-up.

Ineligibility rates, treatment parameters, and protocol deviations will be monitored on a clinic and ophthalmologist specific level. The Principal Investigator of the clinical center will be advised of any problems with the performance of the ophthalmologists in the center. If re-education efforts by the Principal Investigator do not improve performance, certification for the ophthalmologist will be revoked.

### **11.3.1 Specific Requirements for Ophthalmologist Certification for CAPT**

Each ophthalmologist must complete a CAPT general knowledge assessment and an ophthalmologist -specific knowledge assessment to test knowledge of eligibility criteria, treatment protocol, and managing patients during follow-up.

Each ophthalmologist must review cases prepared by the Reading Center and complete the grading form provided with the photographs. The set of photographs consists of both eligible and ineligible patients as well as post treatment photographs to judge treatment intensity.

One set of photographs will be sent to each center to be shared among the ophthalmologists. After all ophthalmologists have completed reviewing the photographs, submitted the grading form, and received confirmation of certification from the Reading Center, the clinic coordinator should return the photographs to the Reading Center. A certification number for each ophthalmologist will be issued by the Coordinating Center after the assessment forms and grading forms have been submitted to and reviewed by the Reading Center.

## **11.4. CERTIFICATION OF CLINIC COORDINATORS**

Clinic Coordinators are responsible for managing patient visits, paperwork associated with the visits, coordination and mailing of photographs, maintaining patient follow-up, and ensuring that information and materials on CAPT are distributed to the appropriate CAPT team members in the clinical center. Clinic Coordinators must be knowledgeable about appropriate procedures for data correction, appropriate people to call in the Coordinating Center and Reading Center to answer questions, procedures for telephone requests for study enrollment and treatment allocation, ensuring that the ophthalmologists have access to needed CAPT documentation, and many other procedural requirements. At the beginning of the study, clinic coordinators are required to attend a training meeting during which they will receive thorough instruction on their responsibilities and specific training in the administration of standardized questionnaires. Individuals who later wish to become clinic coordinators will need to be trained by either the previous clinic coordinator or through conversations with the Project Director and Research Associate.

### **11.4.1 Specific Requirements for Clinic Coordinator Certification for CAPT**

Each clinic coordinator must complete a CAPT general knowledge assessment and a coordinator-specific knowledge assessment to test knowledge of eligibility criteria, procedures required at each visit, visit schedule, and the completion and mailing of forms and photographic materials.

All Clinic Coordinators must complete and submit to the Project Director three Initial Visit Forms, Eligibility Checklists, and Coordinating Center Transmittal Logs and one follow-up form to demonstrate familiarity with these forms and an ability to complete them appropriately.

After submitting these materials to the Coordinating Center, each clinic coordinator will have a certification telephone call with the Project Director. This conversation further assesses the coordinator's knowledge of CAPT protocol and provides an opportunity to discuss CAPT logistics and answer any remaining questions. A certification number will be issued by the Coordinating Center after the knowledge assessments form has been completed, the practice forms have been reviewed, and the telephone call has been successfully conducted.

## **11.5. CERTIFICATION OF VISUAL FUNCTION EXAMINERS**

Visual Function Examiners are responsible for obtaining the data for the primary outcome measure in CAPT and must therefore have a thorough knowledge of the standard procedures for refraction and testing of visual acuity, contrast threshold, and reading speed. During follow-up, the Visual Function Examiner is to be masked to treatment assignment and should therefore have an appreciation of the importance of this design feature, avoid conversations with patients about the management of their eyes, and resist the temptation to examine the patient's clinical chart for information on treatment. Before CAPT certification, candidates must have a basic knowledge of the principles of refraction, acquired from previous instruction or experience.

### **11.5.1 Specific Requirements for Visual Function Examiner Certification for CAPT**

Each Visual Function Examiner must complete a CAPT general knowledge assessment and a visual function examiner-specific knowledge assessment to test their knowledge of the CAPT visual function protocol.

Visual function examiners must identify 3 AMD patients aged 50 or older from the clinic's patient population, one of whom with vision worse than 20/100 in one eye. Visual function examiners must complete the visual function sections of the Follow-Up Visit Form for each of these patients and submit them to the Research Associate. Individuals previously certified in an NEI sponsored clinical trial using procedures nearly identical to those of CAPT, such as the Age Related Eye Disease Study, should contact the Research Associate to obtain a Request for Certification Waiver form. If the waiver is approved, only one form must be submitted to the Research Associate.

After submitting these materials to the Coordinating Center, each visual function examiner completes a telephone interview with the Research Associate on the fine points of each visual function procedure. A certification number will be issued by the Coordinating Center after all requirements have been met.

## 11.6. CERTIFICATION OF PHOTOGRAPHERS

Photographers must demonstrate that they can consistently obtain good quality photographs and stereo angiograms so that the CAPT Reading Center can determine patient eligibility with confidence and determine the status of the features of AMD and other pathology of interest to the study. The photographers will be required to demonstrate their general understanding of the CAPT procedures on the knowledge assessment forms as well as to demonstrate their proficiency in performing the CAPT photography protocol.

### 11.6.1 Specific Requirements for Photographer Certification for CAPT

Each photographer completes a CAPT general knowledge assessment and a photographer-specific knowledge assessment to test their knowledge of the CAPT photography protocol.

If the candidate has been certified in other collaborative studies such as the Macular Photocoagulation Study (MPS), the Age-Related Eye Disease Study (AREDS), the Interferon Study, Submacular Surgery Trials, etc., he/she may qualify for a waiver for some of the certification requirements. Such candidates should contact the Reading Center to obtain a Request for Waiver form.

Candidates who do not receive waivers must submit 6 complete sets (both color photographs and fluorescein angiograms) of photographs obtained according to the Study protocol detailed in Chapter 16. Patients should be chosen from those requiring a fluorescein angiogram for a retinal vascular disease. At least 4 of those patients should have neovascular age-related macular degeneration in at least one eye. Any 4 of the sets should be performed following the protocol for angiography that includes both eyes during the early phase. Negatives of the angiograms submitted for certification are required and will be returned to the clinical center once the requirement of six sets of photographs demonstrating proficiency in performing the photography protocol has been filled. All of the photographs should be labeled according to the Study protocol as well. See Chapter 15 for instructions on labeling and presenting photographs.

Materials for photographer certification should be sent to the CAPT Photograph Reading Center (see the CAPT Address Directory).

After reviewing the color photographs and angiograms, the Reading Center Director makes one of the following judgments:

- The photographs are acceptable and certification is granted.
- The quality of the photographs is marginally acceptable or inconsistent and improvement is necessary. In this case, the Reading Center Director contacts the photographer and discusses the situation. Another 3 to 5 sets of acceptable photographs must be submitted before final certification can be granted.

The Project Director will receive notification when the candidate has successfully completed this aspect of the photographer certification process. When all of the certification requirements have been met the Coordinating Center will issue the candidate a certification number.

### **11.7. CERTIFICATION OF PHOTOGRAPH GRADERS**

Reading Center graders will be certified for CAPT once they have completed the knowledge assessment form and demonstrated a thorough understanding of the CAPT Grading System.

The first phase of the training program includes pathology and anatomy of the eye; identification of features of AMD on stereoscopic color fundus photography as well as on fluorescein angiography; and procedures of the CAPT Grading System. This first phase takes about 3 to 6 months during which time the grader trainee meets bi-monthly with the Principal Investigator, Director and Co-Director to review cases and grading issues. The grader performs the CAPT Grading System on study photographs from both CNVPT and CAPT with constant review and evaluation by the Grading Director.

During the second phase of training, the grader independently performs the CAPT Grading System on study photographs from both CNVPT and CAPT to gain extensive experience. In order to be certified the grader will read a pre-selected set of Training Photographs to demonstrate his/her ability to apply the CAPT Grading System. These gradings will be reviewed with the Grading Director for appropriate interpretation of the photographs as well as for procedural aspects of the CAPT Grading System.

### **11.8. INITIAL CERTIFICATION OF A CLINICAL CENTER**

The Coordinating Center will send to all clinical centers a Site Certification Checklist that lists the requirements to be filled before initiation of patient recruitment. Application for and receipt of institutional review board approval of the clinical trial, acquisition of the testing equipment required for the CAPT protocol, verification that examination rooms have the required lighting levels and testing distances, receipt of the required number of copies of the *Manual of Procedures*, and certification of at least one staff member in each role are among the items listed. Each site of a clinical center must have the equipment and staffing required by the CAPT protocol available on the days that CAPT patients are scheduled for clinic visits to the site.

### **11.9. CERTIFICATION NUMBERS**

The Research Associate will keep a log of certification numbers. Each person will have one CAPT certification number even if he/she is certified for two or more roles. Dates of certification and de-certification for each role are recorded. The Systems Analyst will have online access to the list so that the information may be used in the data editing system to flag any procedure performed by personnel not certified for the position.

## 11.10. MAINTAINING CERTIFICATION

Each year, the Clinic Coordinator will be responsible for verifying that the equipment and space required for CAPT are still available at each certified site. The availability of a full CAPT team at each site when CAPT patients are seen will need to be verified.

Performance monitoring reports, site visit reports, and notes from the quarterly telephone calls will be used by the Clinic Monitoring Committee to identify problems in compliance with the CAPT protocol. Performance at the clinical center, site, and person level will be reviewed. The Project Director and other committee members will be responsible for developing a plan to resolve any performance problem detected. If CAPT certified personnel do not respond positively to the plan for resolution, certification may be revoked. If there are severe problems, the Operations and/or Executive Committees are notified.

### 11.10.1 Re-Certification of Visual Function Examiners

Change in visual acuity is the primary outcome of the CAPT study. It is therefore imperative that Visual Function Examiners consistently demonstrate proficiency at administering all CAPT visual function tests with strict adherence to protocol. To maintain certification, Visual Function Examiners must do the following on a semi-annual basis:

1. At clinical centers with more than one certified visual function examiner, each examiner will independently replicate the examination of another examiner for one AMD patient with visual acuity of 20/100 or worse in at least one eye. The patient tested for replication purposes may be a CAPT patient or another non-study patient at the clinic. Both eyes must be tested and all CAPT visual function tests must be administered. If one patient is unable to undergo a complete set of visual function tests twice, another patient may be used for some of the tests (e.g., reading or contrast sensitivity). However, both examiners must test the same patient(s) for replication purposes. The results of the replicated tests must be submitted to the Protocol Monitor. In addition, each CAPT-certified examiner must observe another examiner administer the visual function tests on an AMD patient with visual acuity of 20/100 or worse in at least one eye. This patient must be different from the patient on whom the tests were replicated. During observation, the observing examiner must have a written copy of the CAPT protocols for visual function testing available and complete a check off sheet provided by the CAPT Coordinating Center.
2. At clinical centers with only one certified Visual Function Examiner, the Protocol Monitor will administer a telephone examination on the fine points of each visual function procedure on a semi-annual basis. In addition, the CAPT-clinic coordinator must observe the visual function examiner administer the visual function tests on an AMD patient with visual acuity of 20/100 or worse in at least one eye. During observation, the observing coordinator must have a written copy of the CAPT protocols for visual function testing available and complete a check off sheet provided by the CAPT Coordinating Center.
3. If, during a six-month period, the Protocol Monitor observes a Visual Function Examiner at a site visit, re-certification requirements are waived for that period.

## CHAPTER 12

### QUALITY ASSURANCE ACTIVITIES

#### 12.1. OVERVIEW

The Coordinating Center has primary responsibility for assuring that the quality of the data collected and reported in the CAPT are of consistently high quality. Many factors contribute to the quality of the data, from the design and procedures of CAPT to the analytic methods employed. The Coordinating Center works with the Reading Center on the design and implementation of a quality assurance program for photographic grading.

#### 12.2. GENERAL QUALITY ASSURANCE FEATURES

The major quality assurance features of the CAPT are:

- Standard data collection forms and procedures;
- Common protocol for eligibility, examination, treatment, and follow-up of all patients in all clinical centers;
- Central treatment allocation with eligibility review preceding enrollment;
- **MASKED** assessment of the primary outcome measure (visual acuity) and the measures of visual function used as secondary outcome measures;
- Central grading of fundus photographs and fluorescein angiograms for eligibility, adherence to treatment protocol, and follow-up status;
- **MASKED** assessment of eligibility and baseline status by graders in the Reading Center and no other indicators of treatment status other than the appearance of the eye during evaluation of photographs taken during follow-up;
- Assessment of health related quality of life using standard instruments and a trained interviewer for those requiring telephone administration;
- Central concurrent processing of data;
- Data editing for missing, invalid, and suspect responses;
- Regular reporting on performance of all centers;
- Concurrent quality control program of the photographic grading system assessing intragrader and intergrader reliability;
- Monitoring visits to all centers;
- Specific data analyses to identify incorrect or fraudulent data collection processes;
- Certification of clinic staff;
- Regular meetings of Investigative Group to review methods and discuss problems.



Coordinating Center staff participate in the design of all data collection forms, coordinate modifications to existing forms, and develop new forms as needed. Since they also supply all centers with master copies of forms, they assure that the current versions of all forms and components are available to the clinical centers.

The members of the CAPT Planning Committee (Drs. Fine, Maguire, Ho and Ms. Javornik) played a major role in developing the protocol and preparing the original *Manual of Procedures*. Coordinating Center personnel and the Director of the Reading Center update the chapters of the *Manual of Procedures*. Coordinating Center personnel are responsible for periodically distributing updates to all centers.

The staff members at the Coordinating Center prepare the treatment allocation schedules for each clinic. They are also responsible for issuing allocations to the clinics by telephone only after explicit verification of eligibility.

Coordinating Center staff members are responsible for all data processing in the CAPT, as described in Chapter 18, and for timely editing, resolution of problems, and reporting. Concurrent data processing is important for providing feedback to each individual involved in data collection and patient care in order to assure that the procedures specified in the protocol are interpreted and applied.

The Research Associate of the Coordinating Center, who is also the Protocol Monitor, has primary responsibility for visiting the participating centers to assist in identifying and resolving problems. Other Coordinating Center staff also assists with these visits as necessary. Staff at the Coordinating Center provides information to the Project Director to facilitate the activities of overseeing clinical center operations.

The Director of the Coordinating Center develops a set of data analytic routines meant to identify patterns in the data that might indicate incorrect or fraudulent data collection processes. Further investigation of these findings will be conducted. Guidelines set by the NEI and the Office of Research Integrity will be followed.

The Project Director is responsible for the certification program for CAPT (see Chapter 11). In addition to the initial training of Clinic Coordinators, the Project Director also organizes and chairs sessions for the Clinic Coordinators at the annual meetings. Problems and issues related to carrying out the protocol are reviewed and discussed to identify methods for resolving problems and improving or easing operations.

The yearly meeting of the Investigative Group is an important method of quality assurance. These meetings provide a means of sharing information among CAPT investigators and personnel. The Coordinating Center staff, with input from the Reading Center and Operations Committee, plays a major role in organizing these meetings and preparing reports and presentations to be made to the Investigative Group.

### **12.3. CLINIC MONITORING COMMITTEE**

The Clinic Monitoring Committee has responsibility for the quality assurance activities required to maintain standardization of procedures and adherence to the CAPT protocol. Membership and specific functions may be found in Chapter 3.6. Problems in clinic performance or adherence to the protocol are normally resolved by the Project Director and Research Associate working directly with the staff of the clinic. When these efforts fail, the problem is referred to the entire committee. If necessary, the Clinic Monitoring Committee reports failure to resolve the issue to the Operations Committee or the Executive Committee.

### **12.4. SITE VISITS TO CLINICAL CENTERS**

Periodic site visits by an independent observer are necessary to assure that there is standardization of procedures, that clinic personnel have been trained adequately, that the clinic facilities meet standards, and that patients and their data are being managed as specified in the protocol. The site visitor also provides assistance in solving logistical problems by conveying efficient, accurate solutions used in one clinical center to other clinical centers. CAPT site visits will begin with a visit within a few months of the initiation of patient recruitment and will then be performed every other year on a staggered schedule.

#### **12.4.1 Scheduling and preparation**

The site visit should be scheduled so that the clinic staff members may arrange their day appropriately, usually a month or more in advance. A copy of the site visit agenda is sent to the principal investigator of the clinic and the clinic coordinator. The site visitor re-arranges the agenda to meet the scheduling constraints of the clinical center.

The site visitor prepares for the visit by reviewing recent site visit reports, notes from recent quarterly telephone calls, and clinic report cards issued by the Clinic Monitoring Committee and makes a list of outstanding issues. The data processing staff prepares data to be checked against clinic forms and original source materials, when available.

The Clinic Coordinator prepares by making sure that patients are available for the site visitor to observe each Visual Function Examiner perform the entire set of refraction and visual acuity, contrast threshold, and reading speed testing. The site visitor may ask the Clinic Coordinator to assist in making arrangements for local lodging and transportation.

#### **12.4.2. Conduct of the visit**

Site visits will generally begin early in the morning and will generally require the entire day. Strict adherence to the protocol is stressed throughout the visit. If clinical center staff view some part of the protocol as unreasonable or difficult to carry out, the clinic staff is instructed to follow the protocol. The site visitor brings the issue to the Operations

Committee, Executive Committee, Director of the Coordinating Center, Director of the Reading Center, or other person as warranted by the particular issue.

General areas of review during the site visit are listed below:

- Clinic staff, facilities and equipment
- Flow of patients through the clinic during initial and follow-up visits
- Up-to-date CAPT documentation including the *Manual of Procedures*, data collection form masters, protocol memoranda, and treatment summary cards
- Observation of Visual Function Examiners
- Observation of the Clinic Coordinator during at least one patient visit
- Storage and access to CAPT patient files, including proper storage of signed consent forms and handling of edit messages
- Discussion of individual patients with follow-up problems
- Brief meeting with at least the lead CAPT Photographer about flow of patients and photographs
- Meeting with the Principal Investigator of the clinic to discuss recruitment, follow-up, and areas of concern

#### **12.4.3. Site Visit Reports**

A written summary prepared by the site visitor will be sent to the Clinic Coordinator, Principal Investigator and members of the Clinic Monitoring Committee. A copy of the report is also maintained in the Coordinating Center library of CAPT documentation.

#### **12.5. REGULARLY SCHEDULED TELEPHONE CALLS**

A telephone call is scheduled once every 3 months (unless a site visit has recently occurred) between the Research Associate and clinic coordinator to make sure that changes (if any) in CAPT personnel, facilities, and equipment have been communicated and that progress is being made in any problem areas of performance. The status of certifications and re-certification requirements are reviewed. The Clinic Coordinators bring any problems, either within the clinical center, or with the Coordinating Center or Reading Center, to the attention of the Research Associate.

## CHAPTER 13

### DATA ANALYSIS AND STATISTICAL ISSUES

#### 13.1. STUDY DESIGN

CAPT is a prospective, randomized clinical trial of laser treatment versus observation within patients with bilateral drusen. Each enrolled person has one eye treated and one eye observed. The eye is the unit of randomization.

#### 13.2. OUTCOME MEASURES

##### 13.2.1. Primary outcome measure

The primary outcome measure for this study is visual acuity. Visual acuity was chosen, rather than the incidence of CNV and the other late complications of AMD, since it will incorporate any negative effects on vision from such developments as increased atrophy as well as the beneficial effects of prevention of CNV. The proportion of eyes with a loss of three or more lines of visual acuity (doubling of the visual angle) will be used in the primary comparison of treated and untreated eyes. Use of mean visual acuity (Log MAR scale) or mean change in visual acuity will most likely be inappropriate for the CAPT data. Eyes that do not develop CNV or geographic atrophy through the fovea will have little change in visual acuity, while the eyes that have these events will have very large losses in vision (MPS [Fellow Eyes], 1993). Over time, this will produce extremely non-normal, asymmetric distributions of both absolute visual acuity and change in visual acuity.

##### 13.2.2. Eye-specific secondary outcome measures

1) The incidence of CNV, geographic atrophy, and serous pigment epithelial detachment will provide a direct measure of the effectiveness of the laser treatment in preventing the late complications of AMD without consideration of visual function. The diagnosis of CNV will be based on color stereo fundus photographs and confirmed with fluorescein angiography. Development of geographic atrophy will be confirmed by color photographs and diagnosis of serous pigment epithelial detachment will be based on color photographs and confirmed with fluorescein angiography.

2) Contrast threshold can be "independent" of visual acuity in patients with AMD in that it does not necessarily change in the same direction as visual acuity (MPS [Subfoveal CNV Trials], 1993). Also, contrast threshold has been shown to be an independent predictor in patients with AMD of the ability to perform several tasks of daily living (Alexander, 1988). Contrast thresholds may worsen because of damage by the laser or may, in fact, improve because of decreases in small pigment epithelial detachments overlying resolving drusen. Contrast threshold scores are recorded to the nearest letter and are on the log scale for arithmetic operations (Elliot, 1991).

3) Comparison of the critical print size for reading between the treated and untreated eyes may detect small functional changes that are not detected by the less "real world" tests of visual acuity and contrast threshold. The critical print size is determined as the print size at which the patient's reading speed decreases. Scoring follows the suggestions of the developer of the test (Mansfield, 1996).

### 13.2.3. Person specific descriptive measures

During the past decade, researchers have generally agreed that optimal health extends beyond traditional clinical markers and patient reported symptoms. The NEI-VFQ-25 has been designed specifically for use in populations subject to visual impairment. The NEI has mandated its use across all of its clinical trials, which will provide a strong base for comparing the relative impact of the common forms of vision threatening disease (Kupfer, 1996). Scoring of the results will follow the recommendation of the developer.

The vast majority of patients will be able to self-administer the QOL instrument during their clinic visits since eligibility criteria require 20/40 or better vision in each eye and only a small proportion (6%) of the patients are expected to have bilateral involvement by the end of the study. Patients who are unable to self-administer the questionnaire will be asked to complete it by having a trained telephone interviewer call them at a convenient time.

## 13.3. SAMPLE SIZE CONSIDERATIONS

### 13.3.1. Approach to Sample Size

The sample size must address the main study question; "Does laser treatment reduce the risk of loss of visual acuity in patients with bilateral high-risk drusen?" Because of the importance of the study, high statistical power (.90) is required. Also, using loss of vision as the primary outcome variable requires a larger sample size than using the incidence of the advanced forms of AMD because the lag time between development and loss of vision reduces the percentage of eyes with loss of vision within a specific period of time.

### 13.3.2. Assumptions for the Sample Size Calculations

Data from the MPS (MPS [Fellow Eyes], 1993) showed that there was virtually no large loss of visual acuity over 5 years for eyes that had not developed CNV (mean change 0.0 lines, 0% with 6 line loss). Thus, even though PEDs and geographic atrophy can be a source of vision loss in these eyes, their actual contribution is negligible. Also, their incidence in that group of fellow eyes was very low, approximately 2% each over a 5 year period.

- The annual *per eye* rate of the late complications of AMD was 4.5% among patients aged 65 years and older with one or more large drusen in the Holz study (Holz, 1994). The weighted average of CNV rates from approximately 1000 AREDS bilateral drusen patients assigned to placebo was at least 3.3%. Weights reflected the proportion of patients enrolled in the Choroidal Neovascularization Prevention Trial (CNVPT) that had specific risk factors for CNV. AREDS rates were only available based on the worst

eye of a patient and on development of CNV in one or two eyes; both of these factors would decrease the rate derived from AREDS for CAPT eyes. An annual rate of 4% per eye was used for the CAPT untreated eyes.

- The percentage of fellow eyes with CNV that had a 3-line loss in visual acuity at 48, 54, and 60 months of follow-up in the recent group of 670 MPS fellow eyes was 77%, 78%, 76% respectively; 75% was used for CAPT (tabulations from the MPS database; laser treatment performed according to the prevalent patient management practices in 1986-92).
- The concordance rate for both eyes in the Bilateral Drusen Study developing CNV was based on independence between eyes in patients having no CNV in either eye (4% per year in observed eyes), and on the fellow eye rate (12% per year in observed eyes) in the years following unilateral involvement. The fellow eye rate was derived by applying the MPS rates of CNV against the risk profile of eyes enrolled in the CNVPT.
- The Fleiss-Levin correction for non-independence in proportions from matched pairs data was used in the Bilateral Drusen Study (Lachin, 1992).
- Type I error rate of 0.05.
- A 16% loss due to death and dropouts over 5 years was used for all calculations. This rate is consistent with those observed in the MPS clinical trials.
- A reduction in event rate by 30% was assumed for effectiveness of the laser in reducing incidence of CNV and loss of 3 or more lines of visual acuity.

### 13.3.3. Sample Size and Power Calculations

Sample sizes were calculated by setting the power at .90 and the alpha level at .05 for detecting a 30% reduction in visual acuity loss. As can be seen in Table 1, 1000 patients will be required.

**Table 1. Sample Size Calculation**

	CNV Incidence	Visual Acuity Loss
<u>Bilateral Drusen Study</u>		
Event Rates: Observed	20.0%	15.0%
Treated	14.0%	10.5%
Concordant	5.9%	4.4%
Power (N = 1000)	.96	.90

## **13.4. DATA ANALYSIS**

### **13.4.1. Statistical Methods to be Applied**

Data analysis will be conducted using standard statistical techniques for comparing two paired groups (Mc Nemar test for equality of proportions, paired t-test, Wilcoxon signed rank test), multiple logistic and linear regression with correlated data (Rosner, 1984, Zeger, 1986, Glynn, 1994), and proportional hazards modeling with correlated data (Therneau, 1990; Lin, 1993,94).

### **13.4.2 Data Analyses of Outcome Variables**

The primary outcome measure is the proportion of eyes with three lines or more of visual acuity loss. The proportion at each point in follow-up as well as the time to this event estimated via survival analysis methods will be examined. If the observed data show recovery of visual acuity from a loss of 3 or more lines, estimation methods for the proportion with loss during follow-up that accommodate recovery (Hillis, 1986; Zeger, 1986) will be used. Exploratory data analysis techniques will be used to examine both absolute and change in visual acuity distributions. Additional summary measures (median, percentage with 6-line loss) will be used to describe the data. Subgroup analyses will be performed to assess the consistency of the data across clinics and levels of important covariates using the regression techniques described above. In particular, subgroup analyses based on the extent of drusen, presence of hyperpigmentation, history of systemic hypertension, history of cigarette smoking, and patient age are planned.

The proportion of eyes with advanced AMD (CNV, avascular PED, or geographic atrophy) will be analyzed as described above for the proportions with 3-line loss. The proportion with CNV only will also be analyzed separately as it is expected to be responsible for the great majority of loss of vision.

Change in contrast threshold and in critical print size will be examined as continuous variables using the mean as the main summary measure, unless inspection of the distribution of data shows highly non-normal data. In that case, nonparametric and categorical summary measures and analyses will be used.

The absolute and change in overall NEI VFQ-25 scores will be analyzed using continuous data techniques. Longitudinal data analysis techniques will be used to describe the pattern of scores over time.

### **13.4.3. Identification of outliers, incorrectly collected data, and possibly fraudulent data**

With each freeze of the database, a set of statistical and data analytic algorithms will be applied to detect data warranting further investigation and/or action. True values of data that are very different from the majority of values are known as outliers and may have undue influence on such statistical procedures as estimating the mean and variance and regression analyses. However, apparent outliers are often attributable to error: data recording error, data entry error, error in recoding in computer programs, error in the way in which the measurement is performed or the question asked. Another source of outliers is fraud.

As part of the preparation for any of the data analyses above, continuous variables, including dates, are subjected to the techniques of exploratory data analysis in order to fully understand the distribution of the variable. SAS, which is the main software package for data analysis, has built in procedures to flag and list values that meet certain criteria for outliers based on the median and interquartile range. The identification number of the patient can be attached to the extreme value. The Director reviews the exploratory analyses and determines whether an investigation of the accuracy of the value should begin. Exploratory analyses are also run for computed variables such as change in visual acuity score. If the outlier values are valid, statistical methods that minimize the impact of outliers will be used.

Other data patterns will also be explored. Dates of clinical procedures will be examined by day of the week to identify the unlikely occurrence of procedures on weekends. Clusters of data values near cutoff values will be investigated. An inordinate percentage of 0 change values may indicate that the values from the last examination were merely copied. When such data patterns are identified, they will be brought to the attention of the Project Director for further investigation.

### **13.5. DATA MONITORING**

The CAPT Data and Safety Monitoring Committee will review a report of performance summaries and treatment comparison data annually (more often if the members so request). The Committee will be presented with a detailed report assessing the baseline comparability of the treatment groups, descriptive and confirmatory statistical analyses of the primary and secondary outcome measures, and adverse events. The Coordinating Center will present a plan for aiding in decisions to stop or continue the CAPT based on use of an O'Brien and Fleming type strategy and the use of stochastic curtailment (conditional power) (O'Brien, 1979). These statistical aids will not be considered binding since many important aspects in the interpretation of the results are not captured by using these statistical techniques.

#### **13.5.1. Statistical guidelines for early stopping because of efficacy**

The general statistical approach to the interim analyses of CAPT data will follow the guidelines first presented by O'Brien and Fleming (O'Brien, 1979) and subsequently expanded by Lan and DeMets (Lan, 1983; DeMets, 1994). The proportion of eyes with a loss of 3 or more lines of visual acuity in each treatment group at each time point in follow-up will be evaluated using longitudinal data analysis methods based on second-order generalized estimating equations (GEE2) (Qaqish, 1992). The GEE2 approach accommodates both the correlation in visual acuity between eyes of the same person and the correlation in visual acuity of the same eye over multiple time points. Additional adjustments to the results of the statistical tests may be needed to accommodate the assumption of independent increments to the data required by the Lan and DeMets procedures (Lee, 1996; Gange, 1996).



For this mode of analysis, information time will be approximated by the cumulative person-years of observation, assuming that the total information in CAPT will be from 5 years of observation on 1000 patients (5,000 person-years). For the meeting in Spring 2000, only 516 patients were enrolled and no patients had 12 months of follow-up. The information time will be less than 4%. Under no condition will CAPT be stopped because of efficacy since no longer-term data by which to assess treatment effects will be available. By Spring 2001, all patients will be enrolled, with approximately 500 having 1 year of follow-up and approximately 120 having 2 years of follow-up (19% cumulative information time) and the trial would be stopped because of efficacy only if there were overwhelming evidence that laser treatment prevented or caused large decreases in visual acuity. Later years would contribute 1000 person years of information (20% information). The time of the anticipated DSMC meetings, the approximate Z-score and corresponding nominal p-value that would be considered the thresholds for stopping the trial for efficacy reasons are noted below. In practice, the O'Brien-Fleming alpha spending rules based on the observed follow-up will be used.

Time	Z	p-value
Spring 2000	N/A	N/A
Spring 2001	4.555	5x10 <sup>-6</sup>
Spring 2002	3.221	.0013
Spring 2003	2.630	.0085
Spring 2004	2.277	.0228
Spring 2005	2.037	.0417

### 13.5.2. Stopping because of Safety

There will be no formal statistical guidelines for stopping because of safety considerations. The interpretation of the incidence of the late complications of age-related macular degeneration and of adverse events is complicated. For example, reports on the natural history of choroidal neovascularization have generally documented gradual to rapid decline in visual acuity, depending on the type of angiographic pattern (classic, occult, or mixed). However, based on the experience in the CNVPT Fellow Eye Study and the observations from the group at Moorfields Eye Hospital in London, it is not clear whether choroidal neovascularization developing after laser treatment causes the same type of decline in vision (Owens, 1999). On the other hand, if many eyes suffered profound, permanent visual acuity loss immediately after the second CAPT laser treatment, prompt action by the Committee would likely be warranted.

### 13.5.3. Other Considerations in Early Stopping

The statistical guidelines described above are only part of any decision to stop a trial early. Additional considerations include:

- Whether the results are consistent among various subgroups of patients and across the various clinical centers;
- Whether the results could be explained by imbalances in the baseline characteristics of the groups;
- Whether the results could be biased by patient or examiner expectations;
- Whether the results are consistent across the primary and secondary outcome measures;
- Whether it is likely that the current trends could be reversed if the trial were to be continued unmodified;
- Whether the medical community would question the validity or strength of the results of the trial because of early stopping.

## CHAPTER 14

### READING CENTER OPERATIONS AND PROCEDURES

#### 14.1. RESPONSIBILITIES OF THE READING CENTER

To facilitate discussion, the responsibilities of the CAPT Reading Center (Reading Center) are given by phase of the clinical trial. The phases may be categorized as initial design and protocol development, final preparation for trial initiation, patient recruitment, patient treatment and follow-up, patient closeout, and final termination of the trials.

##### 14.1.1. Initial Design Phase and Protocol Development

During the initial design phase of CAPT, the Principal Investigator and Directors of the Reading Center, as members of the Planning Committee and leaders in the pilot study, played a major role in:

- Initial testing and refining of the grading system during the pilot study;
- Developing standard photographs illustrating eligibility and treatment criteria;
- Developing standard photographs for identifying pathology to be used by Reading Center personnel;
- Drafting appropriate chapters of the *Manual of Procedures*;
- Drafting the photographic data collection forms;
- Initial testing and refining of the photographic data collection forms and procedures during the pilot study;
- Initial testing and refining of the photographic data processing procedures during the pilot study;
- Participating in the development of procedures for training and certifying staff at the clinical centers;
- Preparing other materials to be used by clinical center staff, such as photograph logs and other auxiliary forms;
- Developing quality assurance procedures for all aspects of the Reading Center.

##### 14.1.2. Final Preparation for the Initiation of the Trial

In order to begin the trial with a fully developed protocol and well-trained staff for all aspects of CAPT, the Reading Center staff performed a number of activities. These activities included:

- Finalizing the protocol details regarding photographic eligibility, identification of exudation at follow-up visits, evaluation of laser treatment and related issues;
- Fine tuning the data collection activities at the Reading Center in conjunction with the activities of the CAPT Coordinating Center;
- Training Clinic Coordinators and Principal Investigators of the clinical centers;
- Certifying photographers and ophthalmologists at the clinical centers;
- Collaborating with the Coordinating Center to refine the editing of photograph grading forms;
- Finalizing the quality control program for photograph grading;
- Collaborating with the Coordinating Center to prepare standard slides for presentations to enhance recruitment.

#### **14.1.3. Patient Recruitment and Treatment and Follow-up Phase**

Activities during this phase can generally be categorized as administrative, data collection and processing, photograph reading, quality assurance, and planning for future phases. Reading Center responsibilities are summarized for each category.

##### *Study Administration*

- Participating in the affairs of each of the standing committees as appropriate;
- Providing the necessary logistical support for all CAPT meetings;
- Establishing communications between the Reading Center and various CAPT centers and committees;
- Assisting the staff at each clinical center to interpret and follow the protocol and procedures relating to the Reading Center as documented in the *Manual of Procedures*;

##### *Material Collection and Processing*

- Maintaining an inventory, tracking, and storage system of all materials received at the Reading Center;
- Confirming that all photographic materials received from the clinical centers are identified and labeled consistently and accurately;
- Conveying the photographic data collected at the Reading Center to the Coordinating Center on a regular schedule;
- Notifying the Clinical Centers of late or delinquent photographs;
- Informing the Coordinating Center of clinical centers that fail to conform to the photography protocols;

*Photograph Reading*

- Performing grading of all study photographs according the established CAPT Grading System in order to:
  - ▶ Document that patients selected for the Study at the various clinical centers meet the angiographic and photographic eligibility criteria specified;
  - ▶ Document that laser photocoagulation treatment performed at the clinical centers on Study eyes assigned to treatment is carried out according to the treatment protocol;
  - ▶ Identify suspected or definite exudation at follow-up;
  - ▶ Interpret the follow-up photographs for status of AMD features and other pathology;
- Determining photographic eligibility of patients prior to randomization at the request of a clinic;

*Data Analysis and Reporting*

- Preparing reports for the Investigative Group concerning the status of receipt of initial visit and follow-up photographs, adherence to the eligibility and treatment protocols, quality of photographs collected, and clinic response to queries;
- Assisting with the development of analytic methods of the photographic data in conjunction with the Coordinating Center;
- Assisting with the preparation of photographic interpretation to be reported in publications from CAPT;
- Participating in the drafting of all CAPT publications;
- Performing other activities deemed appropriate by the Executive Committee, Data and Safety Monitoring Committee, Operations Committee, Clinic Monitoring Committee, or other Study participants as time permits;
- Reporting to appropriate audiences Reading Center methodological innovations developed during the course of the CAPT;

*Quality Assurance*

- Participating in the execution of an initial training sessions for clinic personnel to review study design, data collection methods, and procedures for interfacing with the Coordinating Center and Reading Center;
- Certifying participating ophthalmologists and photographers as competent in the protocol procedures;
- Masking of initial visit photographs as to the randomization assignment until photographic eligibility has been determined;

- Performing Quality Assurance procedures of the CAPT Grading system;
- Performing Quality Assurance procedures of the grading data records;
- Performing Quality Assurance procedures of the inventory of materials received;
- Monitoring the quality of the photographs at all study visits;
- Preparing monthly reports summarizing status of photographs received versus the visits completed at each center;
- Assisting in the preparation of all reports on adherence to protocol in the clinical centers as it pertains to the Reading Center;
- Maintaining documentation of all procedures and operations at the Reading Center;
- Maintaining the photographic files in a secure manner to assure their integrity;
- Backing up the Reading Center data files to assure that data are not lost;
- Reporting periodically on the quality of the data accumulated at the Reading Center;
- Cooperating with any individual or group assigned to review operations at the Reading Center;

#### *Planning for Future Phases*

- Developing procedures for closing out patient follow-up at the appropriate time;
- Planning for permanent, accessible storage of CAPT photographs.

#### **14.1.4. Patient Closeout Phase**

As with earlier phases of CAPT studies, during the Patient Closeout phase the primary responsibilities of the Reading Center staff are concerned with coordination, developing and refining closeout procedures, and data processing and analysis. Specific responsibilities during this period are:

- Assist with familiarizing clinic staff with closeout procedures regarding photography;
- Assist with monitoring adherence to established procedures for patient closeout;
- Assist with developing plans for final editing of photographic data and storage;
- Completing plans for final analysis of photographic data and preparation of publications;
- Developing plans for final disposition of the photographic files;
- Participating in paper writing activities;

### **14.1.5. Termination Phase**

During the last phase of CAPT for which funding is available, the Reading Center may be only minimally funded. The following activities are those anticipated for the Reading Center during this period:

- Responding to any final photographic data queries from the Coordinating Center as required for final data analysis;
- Participating in the completion of manuscripts for publication which may require access to the photographs for illustrations;
- Placing of photographic files and other materials in the selected archives.

## **14.2. ORGANIZATION OF THE READING CENTER**

### **14.2.1. Internal Organization**

Staffing may change as CAPT progresses. The staffing of the Reading Center includes the following roles:

- Principal Investigator (ophthalmologist)
- Director
- Co-Director
- Fundus Photograph Graders
- Administrative Coordinator
- Data Coordinator

The Principal Investigator leads the general scientific affairs of the Reading Center and photograph interpretation responsibilities in particular. The Director has primary responsibility for the day-to-day activities of the Reading Center, while the Co-Director oversees the CAPT Grading System and supervision of the graders.

### **14.2.2. Personnel Responsibilities**

The Principal Investigator is responsible for the overall performance of the Reading Center. Specific responsibilities in this role include:

- Reviews baseline photographs to confirm eligibility of all patients enrolled in the study;
- Collaborates with the Director and Co-Director to maintain and refine the grading program;
- Establishes standards of treatment performance that can be documented photographically;
- Serves as the clinical director of the Reading Center;

- Assists with Reading Center procedural changes involving the interpretation of photographs;
- Organizes research efforts for publications involving Reading Center data and methods;
- Serves as a voting member of the Operations Committee;
- Serves as a voting member of the Executive Committee.

The Director is responsible for the day-to-day operations of the Reading Center. Specific responsibilities in this role include:

- Reviews all baseline photographs to ensure compliance with the photographic and angiographic eligibility criteria and treatment protocols;
- Organizes and supervises daily operations;
- Recruits and trains Reading Center personnel;
- Serves as a photograph reader as needed;
- Serves as a voting member of the Operations Committee;
- Serves as a voting member of the Executive Committee;
- Serves on the Clinic Monitoring Committees;
- Establishes and oversees the Quality Assurance (QA) procedures;
- Assists in training ophthalmologists and clinic coordinators at Study Group Training Meetings;
- Develops a Reading Center Handbook of Procedures;
- Designs appropriate data collection forms;
- Updates Reading Center related chapters in the *Manual of Procedures*;
- Serves as liaison with Coordinating Center regarding Reading Center database issues, photograph interpretation, data queries, and other data collection issues;
- Coordinates the Data Checking Program of Reading Center database;
- Prepares presentations for Study meetings and scientific forums;
- Assists in preparation of general study publications;
- Participates in research efforts for publication of Reading Center methods;
- Administers certification procedures for ophthalmologists to identify eligible patients and perform protocol treatments;
- Supervises certification procedures for study photographers;
- Communicates with clinical centers on issues of patient eligibility and clinic performance;



- Administers Reading Center budget and reviews monthly budget reports;
- Coordinates resolution of photographic data queries from the Coordinating Center;
- Prepares grant continuation and renewals for review and approval by the Reading Center Principal Investigator.

The Co-Director is primarily responsible for the CAPT Grading System. Specific responsibilities include:

- Designs and executes the grader training program to ensure that adequately trained grading staff is available throughout the term of the study;
- Participates in the recruiting and hiring of graders;
- Supervises the graders;
- Performs lead role in refining CAPT grading system;
- Serves as Senior Grader on baseline photographs and treatment photographs as needed;
- Serves as second grader on all gradings as needed;
- Collaborates with the Reading Center Principal Investigator and director regarding clinical interpretation of photographs;
- Assists with communication with clinical centers regarding patient eligibility, advancing stages of AMD, treatment adequacy, complications and criteria for retreatment;
- Administers photographer certification procedures;
- Assists with study publications;
- Assists with presentations at Study Group meetings and scientific forums;
- Participates in the training of ophthalmologists and clinic coordinators at Study training meetings;
- Participates in the Data Checking and Materials Checking programs;
- Participates in the preparation of the Reading Center Handbook of Procedures;
- Serves as liaison with Coordinating Center as needed.

The Fundus Photograph Readers are responsible for the evaluation and interpretation of study photographs according to the procedures in Chapter 17. The specific responsibilities of the graders include:

- Identify inclusion and exclusion criteria on initial visit photographs of patients randomized in the study;
- Evaluate initial visit photographs for detailed description of AMD characteristics;

- Evaluate same-day treatment photographs for adherence to the treatment protocol at initial visit and 12 months;
- Evaluate follow-up visit photographs compared to initial visit photographs for changes in AMD characteristics;
- Identify suspected or definite exudation on follow-up visit photographs;
- Evaluate quality of photographs graded;
- Evaluate photographs for eligibility prior to randomization at the request of clinical centers;
- Evaluate photographs at 12 months for eligibility for additional treatment;
- Resolve photograph grading data queries as identified by the Coordinating Center;
- Participate in QA Grading procedures;
- Participate in data checking procedures of the Reading Center database;
- Participate in Study training meetings;
- Participate in Study Group meetings, and attend Ophthalmologist workshops at those meetings;
- Assist with administrative tasks as needed.

The Administrative Coordinator assists the Principal Investigator, Director and Co-Director with the administrative matters of the Reading Center such as routine correspondence, budget tracking, ordering of supplies, word processing and graphics, and travel arrangements. Additional responsibilities include:

- Interacts with clinical centers regarding photographic materials issues;
- Serves as liaison between the Reading Center data coordinator and the clinical centers;
- Maintains an inventory and obtains duplicate slides for internal use, presentations, and publications;
- Prepares templates of all Reading Center forms and maintains record of all revisions;
- Coordinates the implementation of the QA Grading system;
- Participates in the study training meetings;
- Assists with training of clinic coordinators;
- Supervises the Reading Center data coordinator;
- Prioritizes workload of the Reading Center data coordinator;
- Serves as liaison with Coordinating Center as appropriate;
- Participates in development of Reading Center Handbook of Procedures;

- Participates in Study Group meetings;
- Maintains budget and monthly reporting of expenditures;
- Assists with preparation of annual budget for grant continuation.

The Data Coordinator is responsible for inventory, tracking and storage of all photographic materials received at the Reading Center. Specific tasks are:

- Confirms receipt of all photographic materials received at the Reading Center;
- Checks all materials for completeness and consistency of labeling;
- Notifies clinical centers and resolves any discrepancies of identifying information;
- Establishes Reading Center patient files as patients are enrolled;
- Prepares materials for the grading process;
- Performs data entry of all inventory and grading forms;
- Responds to data queries as appropriate;
- Files and retrieves all study photographs from study files;
- Prepares materials for data checking and materials checking programs;
- Prepares photographs for QA cycles;
- Scans study photographs into computer-assisted grading data base;
- Assists with word processing and graphics as needed;
- Assists all Reading Center staff members as necessary to meet the needs of the Study;
- Attends Study Group meetings.

### **14.3. CONFIRMATION OF ELIGIBILITY BY READING CENTER**

The Reading Center is responsible for determining the eligibility of patients from the initial visit stereoscopic color fundus photographs and stereoscopic fluorescein angiograms after the patient is randomized in the study.

After a patient has been randomized into CAPT, the stereoscopic color fundus photographs of the discs and maculae of each eye and the stereoscopic angiogram including both eyes are labeled and submitted to the Reading Center. Without knowledge of the treatment assignment, the Reading Center Principal Investigator or Director reviews the initial visit photographs for inclusion as well as exclusion criteria prior to a detailed grading by the graders. The photographs are read for eligibility within 2 weeks of receipt. The eligibility evaluation is data entered. The Clinical Center and Coordinating Center are notified when a patient does not meet the eligibility criteria for CAPT.

#### **14.4. PRE-RANDOMIZATION REVIEWS BY READING CENTER**

The purpose of a Pre-Randomization Review is to assist the investigator with the interpretation of photographs of borderline eligible cases, and also to assist in identifying the presence of exclusion criteria.

When the eligibility of a patient is in question, photographs are submitted to the Reading Center along with a Pre-Randomization Review submission form indicating the issue(s) in question. Both color photographs and a fluorescein angiogram are required for the Reading Center to declare the patient eligible for CAPT.

Upon receipt, the Reading Center evaluates the photographs and angiogram for eligibility, and the completed Pre-Randomization form is faxed to the Clinic Coordinator. A 48-hour response time can be expected from the Reading Center. The photographs are returned to the Clinic following the determination. If the ophthalmologist wants to discuss the Reading Center's interpretation, either the Reading Center Principal Investigator or Director are available and can be contacted directly.

#### **14.5. PHOTOGRAPHIC MATERIAL HANDLING AND CONTROLS**

Procedures (as detailed in the Reading Center Handbook of Procedures) are in place to ensure efficient and accurate handling of all materials received at the Reading Center. A summary of these procedures follows.

##### **14.5.1. Receipt and Processing of Photographic Materials**

Photographs of study patients are coded, labeled and presented in slide and negative pages at the clinical centers according to the procedures established in Chapters 15 and 16. The Clinic Coordinators ship the photographs along with the Photograph Inventory Forms and Reading Center Transmittal Logs to the Reading Center.

The Reading Center Data Coordinator receives all materials, checks the forms and labeling of photographs for completeness, and confirms that all information on the materials matches the information on the accompanying forms. Any inconsistencies or discrepancies are resolved before photographs are graded. The Data Coordinator separates the treatment photographs of patients from the initial visit photographs to be evaluated for eligibility. The Data Coordinator secures these treatment photographs until after eligibility has been determined and the initial visit photographs are available for the detailed CAPT grading. See Chapters 15 and 17 for more details.

The Data Coordinator makes the photographs and appropriate grading forms available to the Graders. The Graders read the photographs, complete the grading forms and initial and date each form according to the CAPT Grading System established in Chapter 17.

The Grader returns the photographs and completed grading forms to the Data Coordinator to be checked for completeness of the grading. The Data Coordinator returns any forms with ambiguous, incomplete, illegible or missing information to the Graders for resolution.

The Data Coordinator enters the grading data into the CAPT database and initials and dates the forms indicating completion of the data entry process. The Data Coordinator files the photographs separately from the grading forms within the patient file. Patient files are organized by Clinical Center in patient ID order.

#### **14.5.2. Grading Procedures**

The details of the CAPT Grading System are presented in Chapter 17, Evaluation and Interpretation of Photographs. A senior grader (Director or Co-Director) may serve as a single grader. Otherwise, any two graders grade the photographs independently. Differences are openly adjudicated, and the adjudicated record is data entered. If necessary, the Director or Principal Investigator may be asked to resolve a difficult case. Only the Director or Principal Investigator can declare a patient ineligible for the study. The graders also assess the focus/clarity and stereoscopic quality of all photographs based on their confidence to complete the grading of the photographs.

### **14.6. QUALITY ASSURANCE ACTIVITIES**

The purpose of the Quality Assurance activities of the Reading Center is to ensure the integrity and completeness of the data collected from the evaluation of the photographs and angiograms. These activities include the following:

- Masking Graders to Treatment Assignment
- Reproducibility of Grading
- Automatic edit queries and consistency checks of grading data
- Confirming accuracy of data entry
- Confirming completeness of inventory of photographic materials and their labels.

#### **14.6.1 Masking Graders to Treatment Assignment**

Upon receipt of the initial visit photographic materials, the Reading Center Data Coordinator separates the treatment photographs from the initial visit photographs. These photographs are placed in a secure area until eligibility of the patient has been determined. When the Data Coordinator makes the initial visit photographs available to the graders for the detailed grading following the eligibility grading, he/she includes the treatment photographs.

## 14.6.2 Reproducibility of Grading

### *CAPT Grading System*

The purpose of the Quality Assurance (QA) system is to measure reproducibility of the grading scheme, reproducibility of the graders, and to monitor for grader drift. The procedures involve the regrading of a predetermined set of photographs by each grader at specified times. The results of the QA system identify agreement between graders as well as the reproducibility of each grader.

The QA set of photographs consists of both eyes of 25 patients selected randomly by the Coordinating Center from the first 200 patients enrolled. This set includes a mix of eligible, borderline eligible, and unequivocally ineligible patients, proportionate to the mix of eligibility status of the first 10 months of enrollment. This set also represents a mix of treatment evaluations. The quality assurance set of photographs is graded every 3 months. The set of QA photographs of 25 patients are graded together so that the gradings represent the grader's interpretation at a given period of time. All graders are given the same set of photographs within a specified period of time in order to evaluate inter as well as intra grader variability throughout the study. The original gradings and subsequent gradings of these QA photographs are secured from access by the graders. Details of the QA Procedures are included in the Reading Center Handbook.

The Reading Center Directors and Principal Investigator review results of the QA gradings for discussion with the graders of any needed corrective actions. The results of the QA gradings are reported to the Executive Committee, and to the Data Safety and Monitoring Committee. In addition to the regrading of the QA set of photographs, grading issues are identified on a regular basis and discussed with the graders.

## 14.6.3 Automatic Edit Queries And Consistency Checks Of Grading Data And Corrections

Consistency checks are performed at the time of data entry of Reading Center grading forms. These checks include validation of patient ID numbers, name codes, visit dates and visit codes.

Edit messages are generated to identify inconsistencies within the grading system. These edit messages, generated by the Coordinating Center may result in a confirmation of original grading or the need to correct the original grading. The Reading Center Data Coordinator retrieves the appropriate photographs and grading form from the Reading Center files and presents them along with the edit message to a grader. The grader reviews photographs and decides on the appropriate response. If the grader decides that a change to the grading is appropriate, she/he indicates the change in red on the grading form and initials and dates the change. The grader indicates the corrected data on the edit message and returns the photographs, grading form, and edit message to the Reading Center Data Coordinator. The Data Coordinator attaches the edit message to the grading form, and then makes the correction to the database.

The Coordinating Center must be informed when errors are identified in the grading data at the Reading Center. The grader makes the corrections to the grading form in red and initials and dates the grading form. The source and reason for the error, as well as the original data and corrected data, are indicated on a Data Correction Form. As with an edit message, the Data Coordinator attaches the Correction Form to the grading form and makes corrections to the database.

#### **14.6.4 Confirming Accuracy Of Data Entry**

The accuracy of the data entry system used for the Reading Center gradings is assessed on a monthly basis. A 5% random sample of all Reading Center grading forms is identified for a specified period of time, usually the previous month. The records identified as the sample are printed and checked against the grading forms in the Reading Center files. Discrepancies are noted and corrections made to the data records as appropriate. A report of the frequency and types of errors is provided to the Reading Center Principal Investigator, Coordinating Principal Investigator, and the Coordinating Center Project Director. Details of these procedures are in the Reading Center Handbook of Procedures.

#### **14.6.5 Confirming Completeness Of Inventory Of Photographic Materials And Their Labels**

The accuracy of the inventory of the photographic materials received from the participating clinical centers is assessed on a monthly basis. A 5% random sample of materials received for a specified period of time, based on the data entry of the Photograph Inventory Forms, is assessed. The data records identified as the sample are printed and checked against the Photograph Inventory Forms. In addition, the photographs identified as present on the Photograph Inventory Forms are checked against the photographs in the patient files. At the same time the labels on the photographs are checked for accuracy. Discrepancies are noted and corrections made to the data records as appropriate. Discrepancies that may indicate a recurrent problem are investigated. A report of the frequency and types of errors is provided to the Reading Center Principal Investigator, Coordinating Principal Investigator, and the Coordinating Center Project Director. Details of these procedures are in the Reading Center Handbook of Procedures.

### **14.7. READING CENTER HANDBOOK OF PROCEDURES**

The Reading Center Directors, Principal Investigator and staff are responsible for developing a Handbook of Procedures as a reference document for the Reading Center staff and for others interested in Reading Center operations. The descriptions of procedures included in the Handbook are more detailed than those presented in the relevant chapters of the Study Manual of Procedures and give step by step instructions for each task required to carry out the responsibilities of the Reading Center.

**14.8. READING CENTER STAFF MEETINGS**

The Reading Center staff meets twice a month. The Reading Center Principal Investigator is present at these meetings as needed. Members of the Reading Center staff may attend Coordinating Center staff meetings as appropriate. The purpose of these staff meetings is to ensure the execution of the procedures set forth in the Handbook of Procedures and to set goals for productivity.



## CHAPTER 15

### COLLECTION AND SUBMISSION OF PHOTOGRAPHIC MATERIALS

#### 15.1. INTRODUCTION

All photographic materials submitted to the CAPT Reading Center must be clearly labeled with the appropriate study identification information and accompanied by the appropriate Photograph Inventory Form. Clinic Coordinators will be notified of any missing or discrepant information. Incorrect labeling of photographic materials may require that the materials be returned to a clinical center for corrections. Photographic materials are not considered as “received” by the Reading Center until all information regarding the materials is complete and they are correctly labeled. Photographs are not read until all discrepancies are resolved.

All materials should be shipped in a timely matter. Initial visit photographs are considered late when received more than 15 working days after randomization. Follow-up visit photographs are considered late when received more than 20 working days after date of visit. Initial visit photographs and fluorescein angiogram must be obtained within 28 days prior to randomization. Follow-up visit photographs should be obtained the day of the visit, but must be taken within 28 days of the visual acuity.

#### 15.2. LABELING AND PRESENTATION OF PHOTOGRAPHS

Color photographs at all visits must be labeled with the date of the photographs, the visit type and visit number at the top of each slide mount, and the patient ID number and name code at the bottom of the slide mount. Patient-specific labels will be provided by the CAPT Coordinating Center following randomization. If at any time these labels are not available, information should be printed on the slide mount as shown in Exhibit 15-1. Each slide must also be labeled with an L or R to indicate the left or right slide of the stereo pair.

All color photographs should be placed in side-loading, full (20 pocket), plastic slide sheets with the three-hole punch to the left in the following order: top row- stereo pair of the disc of the right eye, stereo pair of the disc of the left eye. In the second row slides are placed in the following order: stereo pair of the macula of the right eye, stereo pair of the macula of the left eye. To facilitate reading and filing of the photographs, a whole slide sheet should be submitted for each set. Empty pockets in the slide sheet should not be cut off. One slide sheet should not contain photographs of more than one patient, nor photographs for more than one visit.

##### 15.2.1. Presentation of Treatment Photographs

Photographs taken following laser treatment should be placed in a separate slide sheet to facilitate masking the readers to the treatment assignment. If the right eye was treated, the stereo pair should be placed on the left of the slide sheet; if the left eye was treated the stereo pair should be placed on the right. The post treatment color photographs should be placed in the top row, and the red-free photographs in the second row.

### 15.2.2. Labeling and Presentation of Fluorescein Angiograms

Fluorescein angiogram negatives are labeled with the date of the photographs, the visit type and visit number, the patient ID number, and name code. As with the color photographs, patient specific labels will be provided by the Coordinating Center. If at any time these labels are not available, information should be printed on a label as shown in Exhibit 15-1. The label is placed in the upper right-hand corner of the negative sleeve. When more than one roll of film has been used, both negative sleeves containing the film should be labeled. The first negative page should be labeled 1 of 2, and the second 2 of 2. Do not staple the negative sleeves together.

The negatives are placed in negative sleeves starting with the second row so that placement of the study label in the upper right hand corner does not cover any of the images on the film. Blank frames should not be removed from the film. All frames of the roll of film should be submitted. If all the frames of the second roll of film are not used, include a few blanks frames in the last strip of film to indicate the rest of the roll is blank. This is particularly important when the last frames were not taken at 10 minutes. The patient's name should always be removed from the film.

A positive transparency or other form of duplicate angiograms should be prepared prior to submitting the negatives to the CAPT Reading Center. Negatives will not be returned to the clinical centers. If a copy is needed by a clinical center after submission to the CAPT Reading Center, a copy will be made by the CAPT Reading Center with the cost, including shipping, billed to the clinical center. Timeliness of these requests cannot be guaranteed. It is hoped that the number of requests for copies of angiograms will be minimal.

### 15.2.3. Labeling Conventions

The following labeling conventions should be used on all photographic materials:

	<u>VISIT#</u>	<u>VISIT TYPE</u>
Initial Visit	00	IV
Post-Treatment Photographs	00	TR
Post-Treatment at 12 Months Photographs	12	TE
Safety Visit (photographs not required)	03 or 15	SV
Follow-Up Visit	##	FV
Non-Study Visit	XX	NS
Missed Visit	##	MV
Exudative Event	##	EX

(The entry for '##' is determined by the month of the visit: 12, 24, 36 etc.)

### **15.3. INCOMPLETE SETS OF PHOTOGRAPHS**

When a set of color photographs is incomplete, place the slides that are available in the appropriate position on the slide page as described in 15.2. An explanation for the missing photographs should be included in the comments box of the Photograph Inventory Form. If an angiogram is required and is missing, the angiogram label should be placed on the lower row of the color photograph slide page with the words "FA missing" written on it. This should only be done at visits that require angiograms.

### **15.4. STUDY VISIT WITH NO PHOTOGRAPHS**

When photographs were not taken, or were lost or destroyed in processing, a Photograph Inventory Form along with an empty slide page should be submitted to the Reading Center. An explanation for the missing photographs should be included in the comments box. One set of slide labels should be placed on the top right pocket with the word "missing" written on it.

### **15.5. MISSED VISITS**

When a patient misses a visit (time window has closed), a Photograph Inventory Form along with an empty labeled slide page should be submitted to the Reading Center. One set of slide labels should be placed on the slide page on the top right pocket with the word "missing" written on it. The visit type on the label should be crossed out and replaced with MV to indicate missed visit. The change should be initialed according to standard CAPT procedure. A check box is provided on the Photographic Inventory form to indicate a missed visit. This form and slide page can be submitted along with materials of other patients and should be listed on the CAPT Reading Center Transmittal Log along with patients with photographs. The visit is indicated as MV, missed visit.

### **15.6. SAFETY CHECK VISIT**

When photographs are taken at a 3 or 15-month safety visit because the investigator suspects exudation, the photos should be sent to the Reading Center following Exudative Event submission procedures (see section 15.10.3). The photographs can be labeled using CAPT study labels by crossing out the existing visit type and writing SV for visit type and filling in 03 or 15 as the visit number.

### **15.7. NON-STUDY VISIT WITH PHOTOGRAPHS**

When photographs are taken at a non-study visit because the investigator suspects exudation, the photos should be sent to the Reading Center following Exudative Event submission procedures (see section 15.10.3). The photographs are labeled using CAPT study EX labels, and filling in the appropriate month for the visit number.

## **15.8. PHOTOGRAPH INVENTORY FORMS**

A Photograph Inventory Form is to accompany each set of photographs submitted to the CAPT Reading Center. The patient information is confirmed with the Coordinating Center data to ensure that the photographs are correctly identified for each patient visit. The form provides a means to log and track photographs received, and also provides information about the timeliness of the submission of materials. The Data Coordinator at the CAPT Reading Center documents on the form the date materials are received, when there are inconsistencies to be resolved, and the date the photographs are considered complete. This form accompanies the photographs at the CAPT Reading Center until they are prepared for reading, at which time the information is entered into a CAPT Reading Center database, and a grading form is prepared for the readers. The Photograph Inventory Forms are filed by patient ID number in loose-leaf binders at the CAPT Reading Center.

A Treatment Photograph Inventory Form is to accompany each set of photographs obtained following laser treatment. These photographs are kept separate from the regular visit photographs to facilitate the masking of the graders as to the treatment assignment. The Treatment Photograph Inventory Forms are filed by patient ID number in loose-leaf binders separate from the other Photograph Inventory Forms.

## **15.9. CAPT READING CENTER TRANSMITTAL LOG**

The CAPT Reading Center Transmittal Log is used to document materials included in a shipment to the CAPT Reading Center. A separate line is used for each set of photographs submitted, including treatment photographs. A copy is retained at the clinical center in order to identify any missing or partial shipments. The CAPT Reading Center Data Coordinator confirms that the appropriate materials for patient visits listed are included in the shipment. The Clinical Center will be notified whenever any materials are missing, incomplete, or enclosed but not indicated on the log. The CAPT Reading Center Transmittal Logs are filed in chronological order by receipt date by clinic in loose-leaf binders at the CAPT Reading Center.

## **15.10. REQUIRED PHOTOGRAPHS**

### **15.10.1 Initial Visit**

Stereoscopic pairs of the disc and macula (DRS Fields 1 & 2) of each eye are required at the initial visit. Fluorescein angiogram (early phase includes both eyes) is also required. See CAPT Manual of Procedures Chapter 16- Photography for details.

### **15.10.2 Follow-Up Visits**

#### Six-Month Visit

Stereoscopic pairs of the macula (DRS Field 2) of each eye are required at the 6-month visit. If exudation is suspected, a fluorescein angiogram is required as well. Stereoscopic pairs of the discs (DRS Field 1) are not required.

### Annual Visits

Stereoscopic pairs of the macula (DRS Field 2) of each eye and a fluorescein angiogram with the early phase of both eyes are required at annual visits. Stereoscopic pairs of the discs (DRS Field 1) are not required.

#### **15.10.3 Exudative Events**

##### **Exudative Event Identified by the Ophthalmologist:**

When an Investigator identifies exudation on fluorescein angiography, in either or both eyes, a Reading Center Exudative Event Form (INVEVT) is completed and submitted with the color photographs and angiogram to the CAPT Reading Center for each eye in which exudation is identified. The Clinic Coordinator should indicate in section C of the Photograph Inventory Form that an Exudative Event Form is enclosed. The Clinic Coordinator completes section A of the Exudative Event Form. The Investigator completes Section B- Exudation Observed by Ophthalmologist, and the CAPT Reading Center completes Section C- Reading Center Inventory. Upon receipt of materials, the Reading Center will complete an Exudative Event Grading Form. If exudation is not confirmed on the photographs by the Reading Center, the Clinic Coordinator is notified of the disagreement.

##### **Exudative Event Suspected by the Ophthalmologist, but Not Confirmed on Angiography:**

When an investigator suspects exudation at a non-annual visit, fluorescein angiography should be performed. If exudation is not confirmed on the angiogram, the angiogram is still sent to the Reading Center with a Reading Center Exudative Event Form indicating, "exudation not confirmed on FA" for the eye(s) with the suspected event.

##### **Suspected Exudative Event Identified by the Reading Center on Color Photographs:**

When the CAPT Reading Center identifies possible exudation on the color photographs, a Suspected Exudative Alert Form is faxed to the Clinic by the Reading Center. The Clinic Coordinator is instructed to pull the photographs from the patient's CAPT file and present them along with the Suspected Exudative Event Form to the ophthalmologist. If the ophthalmologist agrees that there are signs of exudation present, the patient should be scheduled for a visit to obtain color photographs and a fluorescein angiogram with the early phase of the eye with suspected exudation.

If the ophthalmologist identifies exudation on the angiogram, the Clinic Coordinator should:

- Submit a Reading Center Exudative Event Form to the Reading Center along with the photographs and angiogram.
- Submit a Clinic Exudative Event Form to the Coordinating Center.
- Return the Suspected Exudative Event Response Form to the Reading Center.

If the ophthalmologist disagrees that there are signs of exudation on the color photographs, only the Suspected Exudative Event Response Form is returned to the Reading Center.

### **Exudative Event Identified by the Reading Center on Fluorescein Angiography:**

When the CAPT Reading Center identifies an exudative event on fluorescein angiography, an Exudative Event Alert Form is faxed to the Clinic by the Reading Center. The Clinic Coordinator is instructed to pull the photographs from the patient's CAPT file and present them along with the Exudative Event Alert Form to the ophthalmologist for review.

If the ophthalmologist agrees that there is exudation present, he/she should consider appropriate treatment options.

The Clinic Coordinator should:

- Submit an Error Correction Form to the Coordinating Center to correct section V. of the Follow-up Visit Form associated with these photographic materials, since an exudative event for the indicated eye was not originally recorded.
- Submit a Clinic Exudative Event Form (801.1) to the Coordinating Center.
- Return the Exudative Event Response Form to the Reading Center.

If the ophthalmologist disagrees that there is exudation present, the Clinic Coordinator returns only the Exudative Event Response Form to the Reading Center. The ophthalmologist may choose to discuss the case with the Reading Center.

#### **15.10.4 CNV Treatment at Month 12**

When a patient has focal laser treatment at month 12, a color stereo pair and a red-free stereo pair of the macula should be taken within 48 hours following treatment.

#### **15.10.5 Treatment of CNV**

When an eye receives treatment for CNV at any time during the study, post-treatment photographs are not required.

#### **15.11. SHIPMENT OF MATERIALS**

All shipments should be sent in a large envelope so that the slide pages, negative sleeves and forms are not folded or bent. Each shipment should include:

- CAPT Reading Center Transmittal Log- listing each visit included
- Photographic Inventory Forms- one for each set of photos
- Slides properly labeled and appropriately presented on the slide page
- Angiograms (when required) appropriately labeled and presented in the negative sheet

Copies of all photographs, angiograms and forms should be retained at the clinical center in the patient study files.

All materials must be shipped in a timely manner. Initial Visit photographs are considered late when received more than 15 working days after randomization; 20 working days after the date taken for a follow-up visit.

All materials should be shipped to:

Data Coordinator  
CAPT Reading Center  
3535 Market Street, Suite 700  
Philadelphia, PA 19104-3309

#### **15.12. READING CENTER NOTICES**

Whenever there is missing, discrepant, or incomplete information on the photographs, angiograms, Photograph Inventory Form, or Reading Center Transmittal Log, a CAPT Reading Center Notice may be issued. This notice will be sent via FAX to the Clinic Coordinator identifying the problem, with instructions as to the resolution of the problem.

There may be circumstances when the photographs will be returned to the Clinic Coordinator. A CAPT Reading Center Notice will be sent via FAX to the Clinic Coordinator as notification that the photographs are being returned, the reason, and instructions for resolving the problems. A copy of this notice will be included with the photographs.

Materials are not recorded as complete until all problems are resolved. Photographs are not read until they are complete; therefore, it is important that all CAPT Reading Center Notices are responded to in a timely manner.

#### **15.13. SUBMISSION OF PRE-RANDOMIZATION REVIEWS**

Photographic materials may be submitted to the Reading Center for a Pre-Randomization Review to assist the investigator with the interpretation of borderline eligible cases, and to assist in identifying the presence of exclusion criteria (see section 14.4). A Pre-Randomization Review Form indicating the reason for submission must accompany each set of photographs.

Color stereoscopic photographs of the disc and macula of each eye, as well as a fluorescein angiogram are required for the Reading Center to declare the patient eligible. Color photographs are submitted in a plastic slide sheet following the protocol for presentation of study photographs (see section 15.2). The slides are labeled with the patient name code, clinic #, and date of photographs. Fluorescein angiogram negatives are presented in negative sleeves according to study protocol (see section 15.2), and each sleeve is labeled with the patient name code, clinic #, and date of photographs.

The required photographs and completed Pre-Randomization Review Form are shipped to the Reading Center following the directions in section 15.11. Note however, it is not necessary to submit a CAPT Reading Center Transmittal Log or Photograph Inventory Form with a Pre-Randomization Review.

## CHAPTER 16

### PROCEDURES FOR FUNDUS PHOTOGRAPHY

#### 16.1 INTRODUCTION

Good quality photographs are necessary to describe pathology present and to determine whether the eye meets the eligibility criteria. High photographic standards have been established and maintained to prevent otherwise eligible patients from being rejected from the study because of an inability to interpret photographs of poor quality. Photographic techniques have been developed to ensure high photographic quality, standardization of camera equipment, and film development.

In addition, photographers at the clinical centers must demonstrate that they understand the photography protocol and can achieve good quality photography. Certification requirements for photographers can be found in CAPT Manual of Procedures Chapter 11.

All photographs must be taken no more than 28 days prior to randomization. Follow-up visit photographs must be taken within 28 days of the visual function testing.

#### 16.2 CAMERA EQUIPMENT, FILM, AND FILM PROCESSING

- Zeiss 30<sup>0</sup> or Topcon 35<sup>0</sup> fundus photograph cameras with 2.5x to 3x magnification should be used for both color photographs and fluorescein angiograms.
- Tri-X or Tmax film should be used for fluorescein angiograms. Color photographs may be taken with either Kodachrome or Ektachrome color slide film; however, the processed film from Initial Visit photographs must be received at the Reading Center within 15 working days. Variances have been granted for use of Fujifilm Neopan 400 black and white film for angiograms, and Fujifilm Sensia color film for CAPT color photographs. Imation/Scotchchrome is not acceptable. Since there may be a slight difference in the color balance of different films, the Reading Center investigators recommend that whenever possible the same film type be used for all photographs for a patient.
- Delori or Spectratech filters should be used for excitation and barrier filtration: SE-40 Excitation, SB-50 Barrier. These filters should be changed every 24 months, or when inspection at a site visit proves them to be defective.
- Since the original angiographic negatives are submitted for reading, it is recommended that a high contrast developer be used in order to maximize capillary detail. Kodak D-11, diluted 1:1, should be used at approximately 70<sup>0</sup> F for eight minutes. A variance has been granted to use Kodak HC-110, dilution A, at 75<sup>0</sup> for six minutes. The exact processing time and temperature can be adjusted by the participating center to compensate for differences in cameras and to provide negative density acceptable to the Reading Center.
- Color red-free photographs, taken with a Spectratech 540 nanometer filter, are required following treatment, in addition to color photographs, in order to delineate more clearly treatment boundaries and vessel patterns. The Kodak gelatin filter is not acceptable.



- A cone should not be used in the camera, as some information in the area of eligibility may not be visible when a true field 2 is not taken.

### 16.2.1 Modification to Photographic Technique

Acceptable results can be obtained with different development techniques and different films. The continuing advancements in hardware make it possible to say that these recommendations are, in every case, optional and will remain that way throughout the course of CAPT. Therefore, the following provisions are made for exceptions and revisions to this protocol.

- If a photographer at a participating clinical center believes that there is just cause for deviation from protocol he/she may apply to the Reading Center for a variance. The application should include a letter of explanation, and several sample photographs produced by the proposed method. If the Reading Center agrees that the standards of the Study are upheld, the variance will be granted.
- If the Reading Center staff identifies methods that they consider superior to those in use, those methods will be presented to the participating photographers for implementation.

### 16.3 COLOR FUNDUS STEREOGRAPHY

Color stereoscopic fundus photographs are to meet the criteria for field definition as described in the DRS Seven Standard Fields of the Fundus. (See Exhibit 16-1).

#### 16.3.1 Required Fields

The color stereoscopic fundus photographs of the disc (DRS Field 1) and the macula (DRS Field 2) of each eye are required at the initial visit. Color stereoscopic photographs of the macula *only* (DRS Field 2) of each eye are required at 6-month follow-up and annual visits.

Immediately after treatment, color stereoscopic and red-free color stereoscopic photographs of the macula of the treated eye should be taken.

#### 16.3.2 Evaluation of Quality

The quality of the photographs is determined at the Reading Center based on the confidence of the reader to complete the grading form. The focus/clarity of the photograph and stereopsis are evaluated separately for each eye according to the following criteria:

##### **Focus/ Clarity:**

**Good** - All questions on the grading form that require color photographs can be answered.

**Fair** - Reduced quality of the color photograph interferes with the ability to answer one or more questions on the grading form.

**Poor** - Unacceptable quality that precludes completing all or part of the grading form requiring color photographs.

**Missing** -No color photographs are available for the visit.

**Stereopsis:**

- Good** – Obvious stereo separation is present, and all questions on the grading form that require stereopsis can be answered.
- Fair** – Questionable stereo separation is present. Reduced quality of stereopsis interferes with the ability to answer one or more questions on the grading form.
- Poor** – No stereo separation is present which may preclude completing all or part of the grading form requiring stereopsis. For example, stereopsis is required to determine the presence or absence of a serous pigment epithelial detachment.
- Missing** -No color photographs are available for the visit or one side of a stereoscopic pair is missing.

**16.4 FUNDUS FLUORESCIN ANGIOGRAPHY**

All fluorescein angiograms should be taken in stereo unless precluded by media problems or borderline pupillary dilatation. Use of the stereo separator is permissible providing that it does not diminish the quality of photography. The sequences of the required fields of each eye are described in 16.4.2. The sequence with the early phase including both eyes is followed for the initial visit and annual visits. At follow-up, when exudation is suspected in one eye, the sequence with the early phase on the eye with suspected exudation is followed.

**16.4.1 Fluorescein Injection**

Five cc of 10% sodium fluorescein should be injected into the antecubital region with a 19 or 21 gauge Butterfly infusion set with a push no longer than 6 seconds in duration. In some patients, the use of 1 cc of 25% fluorescein followed by a saline flush may provide better resolution of the perifoveal capillary net.

**16.4.2 Sequence For Fluorescein Angiography****16.4.2.1 Sequence with early phase of both eyes:**

Prior to fluorescein dye injection, black and white red-free stereo photographs should be taken of the macula of each eye. Begin with the right eye by taking 3 stereo pairs of the macula at 20-35 seconds. Then immediately go to the left eye to take stereo pairs of the macula between 45-50 seconds and again at 60 seconds. Immediately after this, return to the right eye for stereo pairs of the macula between 70-75 seconds, and again at 90 seconds. Return to the left eye for stereo pairs of the macula between 100-110 seconds and again at 120 seconds. Return to the right eye for stereo pairs of the macula between 130-140 seconds and again at 3 minutes. Return to the left eye to take a stereo pair of the macula at 3 ½ -4 minutes. Change film. Begin the second roll of film by taking stereo pairs of both the macula and disc of the left eye between 5-5½ minutes. Then immediately go to the right eye for stereo pairs of both the macula and disc at 5 ½ -6 minutes. Remain in the right eye to take a stereo pair of the macula at 10 minutes and finally a stereo pair of the macula of the left eye at 10 ½ minutes.

### 16.4.2.2 Sequence with early phase of one eye:

If exudation is suspected or known, the following protocol must be followed:

- Prior to the fluorescein dye injection, black and white red free stereo photographs of the macula of both eyes
- Eye with suspected or definite exudation: Stereo pairs of the macula taken at 30, 40, 60 and 90 seconds and 2, 3, 5 and 10 minutes and stereo photographs of the disc taken at anytime after 2 minutes
- Eye without CNV: Stereo pairs of the macula taken after 2 minutes and at 5 and 10 minutes, and stereo disc photos taken anytime after 2 minutes

Note: A second roll of film may be required to obtain all of the required frames.

### 16.4.3 Evaluation of Quality

The quality of the fluorescein angiogram is determined by one reader at the Reading Center. The quality of the angiogram and stereopsis are evaluated separately for each eye according to the following criteria:

#### Focus/Clarity:

*Good* - The entire grading form can be completed, all necessary frames are present.

*Fair* - One or more pairs are missing or the quality of the stereo makes grading difficult.

*Poor* - The required angiogram frames are missing or the quality precludes answering one or more questions on the grading form.

*Missing* - No angiogram is available for grading.

#### Stereopsis:

*Good* - All questions on the grading form that require stereopsis can be answered; all necessary pairs are present.

*Fair* - One or more pairs are missing or the quality of the stereo makes grading difficult.

*Poor* - The required stereo pairs are missing or the quality of the stereo precludes answering one or more questions on the grading form.

*Missing* - No angiogram is available for grading.

## 16.5 REQUIRED PHOTOGRAPHS BY VISIT

A summary of the required photographs by visit can be found in Exhibit 16-3.

### 16.5.1 Initial Visit Photographs

At the Initial Visit, stereoscopic color photographs of each disc and macula of both eyes should be taken for all patients. A fluorescein angiogram is required at Initial Visit with the early phase including both eyes. The color photography and the fluorescein angiograms must be  $\leq 28$  days old at time of randomization.

### 16.5.2 Same-Day Laser Treatment Color Photographs

Stereoscopic color photographs and stereoscopic red-free color photographs of the macula of the treated eye only are taken the same day as treatment. If the treatment photographs cannot be taken the same day as treatment, they may be obtained up to 48 hours after treatment. If all of the laser burns are not visible in the Field 2 photographs, additional stereoscopic photographs may be taken. This should be the exception if the treatment protocol is followed.

#### 16.5.2.1 Patient Preparation for Same-Day Laser Treatment Photographs

To obtain gradeable same-day laser treatment photographs, the treated eye should be thoroughly rinsed out with sterile saline immediately after any treatment when Goniosol (methyl cellulose) is used. Even if the ophthalmologist has rinsed out the eye, either the Coordinator or the Photographer should follow the procedures listed below to ensure a clear view for the same-day laser treatment photographs.

1. Have the patient tilt his/her head back, not beyond a comfortable level.
2. Have the patient hold several tissues under the eye.
3. Have the patient look down and gently lift the upper lid slightly away from the eye.
4. Rinse thoroughly under the eyelid. This is where the Goniosol stays trapped and each time the patient blinks, the view becomes hazy and blurred again. This method may be a bit messy if the patient does not hold the tissues under the eye.
5. Repeat step 4 for the lower lid.

If the photographer finds that the retinal image is still blurred, possibly from the Goniosol, the rinsing procedure should be repeated.

### 16.5.3 Follow-up Visits

For all patients, stereoscopic color photographs of the macula only of both eyes should be taken for all patients at 6, 12, 24, 36 48, and 60 months. In addition, a fluorescein angiogram with early phase of both eyes is obtained at all annual visits. In cases when exudation is noted or is suspected at any non-annual visit, a fluorescein angiogram must be obtained. The sequence with the early phase including one eye should be followed for the eye with suspected or obvious exudation.

### 16.5.4 Treatment of CNV

When an eye receives treatment for CNV at any time during the study, post-treatment photographs are not required.

## 16.6 USE OF UNCERTIFIED PHOTOGRAPHER FOR CAPT PATIENTS

CAPT Clinic Coordinators are responsible for ensuring that CAPT-certified staff is available when CAPT patients are at the clinic for CAPT appointments. In the rare instance when it is impossible to obtain photographs by a certified photographer, the following steps should be taken:

1. The Coordinator should review the photography protocol with the available photographer, noting in particular the fact that the CAPT protocol requires that the early phase of the angiogram includes stereo pairs of both eyes. They should also review also the fact that there are two sets of photographs taken after treatment, both color and color red-free stereo pairs of the treated eye. If there are any questions, the Clinic Coordinator should encourage the photographer to contact the Reading Center.
2. The name of the photographer is filled in on the "Photographs" section of the CAPT Visit Form, and the code "9999" is used for photographer certification number.
3. The Photograph Inventory form should have the photographer's name printed in the "Comments" box, along with the reason the CAPT certified photographer was not available. The code "9999" is again used for photographer certification number.

## Exhibit 16 - 1

### REQUIRED FIELDS\* OF THE FUNDUS

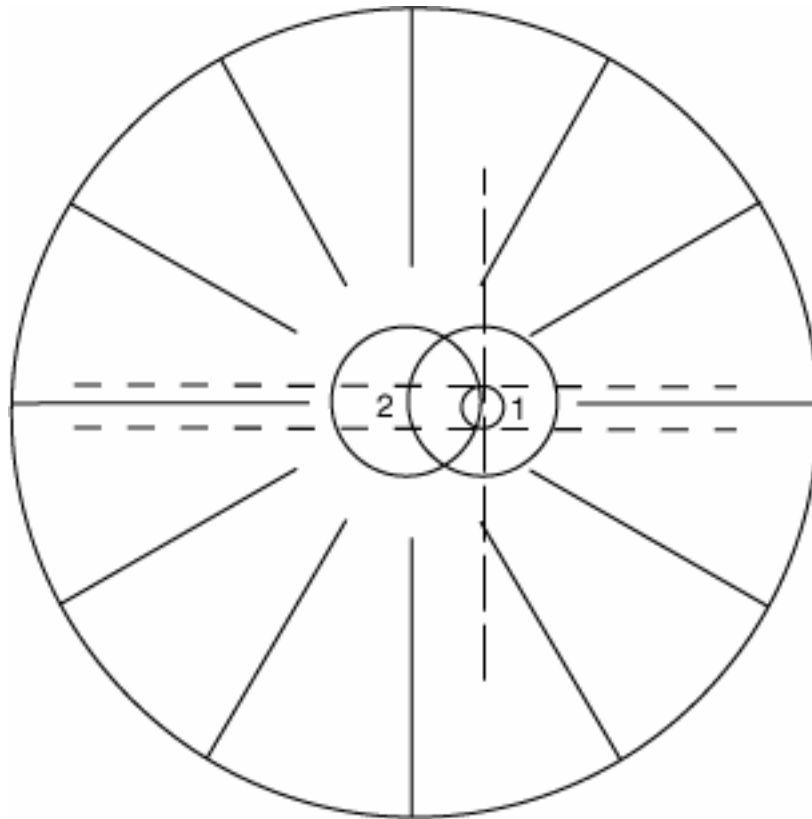
The two standard fields of the fundus are defined and illustrated for the right eye. This description assumes that there are two cross hairs in the camera ocular, one vertical and the other horizontal.

#### *Field 1 - Disc*

Center of optic disc at intersection of hairs in ocular.

#### *Field 2 - Macula*

Center of macula at intersection of cross hairs in ocular\*\*.



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\* Diabetic Retinopathy Study Research Group: Diabetic Retinopathy Study Report Number 6. Design, methods, and baseline results. *Invest Ophthalmol Vis Sci* (1, pt 2): 149-209, 1981.

\*\* In practice, to keep the central gray artifact created by the camera from obscuring the center of the macula, the intersection of the cross hairs should be placed about  $\frac{1}{8}$  to  $\frac{1}{4}$  disc diameter to either side of the center.

## Exhibit 16-2

# CAPT Fluorescein Angiography Protocol (Early Phase of Both Eyes)

Stereo pairs should be shot in *reverse* (right side first) for correct viewing on an uncut film strip.

### RIGHT EYE

Stereo Red Free Macula

Begin / End Injection

20-35 Seconds: 3 Stereo Pairs Macula

70-75 Seconds: Stereo Pair Macula

90 Seconds: Stereo Pair Macula

130-140 Sec: Stereo Pair Macula

3 Min: Stereo Pair Macula

5.5-6.0 Min: Stereo Pair Macula and Disc

10 Min: Stereo Pair Macula

### LEFT EYE

Stereo Red Free Macula

45- 50 Seconds: Stereo Pair Macula

60 Seconds: Stereo Pair Macula

100-110 Seconds: Stereo Pair Macula

120 Seconds: Stereo Pair Macula

3.5-4.0 Min: Stereo Pair Macula

### CHANGE FILM

5.0-5.5 Min: Stereo Pair Macula and Disc

10.5 Min: Stereo Pair Macula

Exhibit 16-3

**CAPT Fluorescein Angiography Protocol**  
**(Early Phase of One Eye)**

Stereo pairs should be shot in reverse (right side first) for correct viewing on an uncut film strip.

FIRST EYE

SECOND EYE

Stereo Red Free Macula

Stereo Red Free Macula

Begin / End Injection

30, 40, 60, 90 sec., 2 min.: Macula Stereo Pairs

After 2 minutes: Macula Stereo Pair

3 minutes: Macula Stereo Pair, Disc Stereo Pair

Between 2 & 5 minutes: Disc Stereo Pair

CHANGE FILM

5 minutes: Macula Stereo Pair

After 5 minutes: Macula Stereo Pair

10 minutes: Macula stereo pair

After 10 minutes: Macula Stereo Pair



**Exhibit 16-4**  
**Summary of Required Photography**  
**By Visit**

Initial visit:

- Color stereo photography: Disc and macula, both eyes.
- Fluorescein angiography: Early phase of both eyes
- Color stereo photography and red-free stereo photography: Macula of treated eye only, same-day as laser treatment (Initial treatment and retreatment)

Follow-up Visit: 6 months

- Color stereo photography: Macula, both eyes
- Fluorescein angiography: Only required for suspected or definite exudation. Early phase on eye with exudation; if exudation in both eyes, follow early phase to include both eyes. Note: If no exudation is present or suspected, no angiography is performed.

Annual Follow-up Visits

- Color stereo photography Macula, both eyes
- Fluorescein angiography: Early phase of both eyes

Exudation (Confirmed or Ruled Out) at Any Visit:

- Color stereo photography: Macula, both eyes
- Fluorescein angiography: Early phase on the eye with suspected or definite exudation

Laser Treatment for CNV:

- Eye had confluent laser treatment for CNV at any time during the study: color stereo photography and red-free color photography of treated macula same-day as treatment, in addition to pre-treatment photography

**Exhibit 16-5  
Required Photographs by Visit**

	Color Stereo Photographs		Red-Free Color Stereo Photographs	Fluorescein Angiography (With early phase of:)	
	Disc	Macula	Macula	Both Eyes	One Eye
<b>Initial Visit</b>	<b>OU</b>	<b>OU</b>		<b>X</b>	
<b>After Treatment*</b>		<b>X*</b>	<b>X*</b>		
<b>6 months</b>		<b>OU</b>			
<b>12 months</b>		<b>OU</b>		<b>X</b>	
<b>After Treatment at 12 months*</b>		<b>X*</b>	<b>X*</b>		
<b>24 months</b>		<b>OU</b>		<b>X</b>	
<b>36 months</b>		<b>OU</b>		<b>X</b>	
<b>48 months</b>		<b>OU</b>		<b>X</b>	
<b>60 months</b>		<b>OU</b>		<b>X</b>	
<b>Confirmed or Suspected Exudation**</b>		<b>X**</b>			<b>X</b>

**\* Photographs only of the eye which was treated.**

**\*\* Photographs only of the eye in which exudation is confirmed or suspected at a non-annual visitb.**

## CHAPTER 17

### EVALUATION AND INTERPRETATION OF PHOTOGRAPHS

#### 17.1 INTRODUCTION

The CAPT grading system has been developed to incorporate already established classifications of AMD, as well as the evaluations necessary to achieve the goals of the Reading Center for CAPT. Two classification schemes, The Wisconsin Grading System (Klein, Davis et. al, 1991) and the International Classification and Grading System for Age-Related Maculopathy and Age-related Macular Degeneration (International ARM Epidemiological Study Group, 1995) serve as the basis for the grading of drusen and the atrophic conditions of AMD. Color stereoscopic Diabetic Retinopathy Study Photographic Standard Fields 1 (centered on the disc) and 2 (centered on the macula) are required of both eyes of all CAPT patients at the initial visit, and only field 2 at all follow-up visits. A fluorescein angiogram with the early phase including both eyes is required at all annual visits to monitor for exudation.

The CAPT Grading System methodology is designed to allow comparisons of the CAPT study population and its clinical recommendations and findings with other AMD populations being studied using epidemiological cross-sectional surveys of AMD. In other words, this grading system affords the ability to determine the relevance of CAPT findings to free-living populations afflicted by AMD.

Detailed fundus grading of both eyes is performed at the time of the initial visit with a modified grading performed at follow-up visits. The majority of the descriptions in the CAPT Grading System, as well as some of the CAPT Standard Photographs are derived from the September 1996 version of The Wisconsin Age-Related Maculopathy Grading System.

##### 17.1.1 Goals

The goals of the grading system are to:

- Confirm eligibility of patients randomized in CAPT
- Identify complications of treatment
- Monitor adherence to the treatment protocol
- Describe the AMD characteristics of each eye at initial visit
- Record changes in AMD characteristics at follow-up visits
- Identify exudation and record changes in exudation at follow-up visits

##### 17.1.2 Standard Procedures

1. Photographs are not presented to the readers until any discrepant or missing information on the Photograph Inventory Form or photograph labels has been resolved.

2. All baseline eligibility evaluations are reviewed by the Reading Center Principal Investigator or Director. Any eyes determined to not meet the eligibility criteria are reviewed by the Reading Center Principal Investigator.
3. Only after the eligibility has been determined are the treatment photographs made available for grading.
4. Two readers independently grade the photographs, with discrepancies openly adjudicated. Only the adjudicated record is data entered. A senior level reader may complete some gradings without a second reader.
5. The readers also assess the quality of the photographs.

### 17.1.3 Quality Assurance

The Quality Assurance (QA) System involves the regrading of a predetermined set of photographs to test for reproducibility of the grading scheme and the reproducibility of each reader, as well as to monitor for reader "drift" in interpretation.

Three times a year the Data Coordinator will provide *each* reader with the same set of photographs, which have been selected as the QA set. This set of 25 patients' photographs will include Initial Visit, Treatment, Retreatment, and Follow-up. The set of QA photographs will be presented to *each* reader to be graded together. The readers will not have access to previous gradings of the photographs. The QA grading forms are returned to the Data Coordinator for data entry to an identified QA database.

## 17.2 INITIAL VISIT ELIGIBILITY EVALUATION

The Reading Center determines final eligibility for patients enrolled in CAPT (CAPT Baseline Eligibility Evaluation Form). The determination is made from the evaluation of an initial visit fluorescein angiogram and color stereo macular photographs. The patient's identifying information, date of photographs and quality of photographs are recorded. The Reading Center Director or the Principal Investigator confirms all eligibility determinations.

The eligibility review confirms that 10 or more drusen ( $>125\ \mu\text{m}$ ) within  $3000\ \mu\text{m}$  of the foveal center are present in each eye. CNV, serous pigment epithelial detachments, geographic atrophy within  $500\ \mu\text{m}$  of the foveal avascular zone, geographic atrophy  $>1$  MPS disc area, or any other ocular disease affecting vision disqualify the patient. If a condition is present that does not affect eligibility, then it is recorded under "other condition".

## 17.3 GENERAL CONSIDERATIONS

### 17.3.1 Subdivisions of the Fundus

The Wisconsin standard grid (Klein, Davis et. al, 1991), consisting of three circles concentric with the center of the macula and four radial lines, is superimposed over one member of the stereo pair of Field 2. Because of the magnification produced by the fundus camera, 4.7 mm on the grid corresponds to approximately  $1500\ \mu\text{m}$  in the average fundus. The stereo viewer

increases the approximately 3X magnification on the film by 5X, resulting in total magnification of 15X. The radius of the innermost (central) circle corresponds to 500 $\mu$ m in the fundus of an average eye, while the radii of the middle (inner) and outer circles to 1500 $\mu$ m (approximately one disc diameter) and 3000  $\mu$ m, respectively. Two segments of a horizontal line are also included to facilitate placement of the grid. Although this grid delineates nine subfields, the CAPT Grading System will grade most fundus characteristics in 3 separate concentric zones (central subfield with radius of 500 $\mu$ m, inner subfield between 500 and 1500  $\mu$ m radii, and outer subfield between 1500 and 3000  $\mu$ m radii) and some characteristics in aggregate. The grid is placed routinely over the best quality photograph of the stereo pair to be graded.

#### 17.3.1.1 Grid Placement

To place the grid, the reader identifies the center of the macula first. Consideration is given both to the increased pigmentation that usually surrounds it and the pattern of the smallest visible perifoveal blood vessels, which approach but do not reach it. A compromise may be necessary when these landmarks suggest different points as the center.

The relationship of the center of the macula to the disc is usually the same for each of a participant's eyes, and this may be helpful when good landmarks are present in one eye but not the other. When the landmarks described above cannot locate the center of the macula, the grid should be placed so that its center is approximately 2 disc diameters temporal to the disc margin.

The grid is permanently placed on each image electronically. The better frame of the pair is chosen and scanned into the computer. The digital image is then labeled with the patient ID# and Name Code, and the date of the photograph. A reader uses the Reading Center Computer Assisted Fundus Evaluation (RC\_CAFÉ) software to center the grid and create a permanent image. The image with the grid is then converted into a slide, which is placed back into the slide page as part of the original stereo pair. The original slide that was scanned is retained on the slide page for future reference.

#### 17.3.2 Standard Circles

Three sets of open circles (designated "C" for central, "I" for inner, "O" for outer subfields) are used to estimate size of drusen, area involved by drusen, and area involved by increased pigmentation. The CAPT Grading System utilizes the set of open circles designated "C." (Klein, Davis et. al, 1991)

For grading drusen size, circles C-0, C-1 and C-2 are used for all subfields. The approximate diameters in the average fundus are 63  $\mu$ m, 125  $\mu$ m, and 250  $\mu$ m respectively.

For grading the area involved by drusen, or for grading the area of focal hyperpigmentation, circles C-1 and C-2 are used in all subfields.

For defining smallest area of involvement that defines the presence of geographic atrophy Circle C-2 is used.

## 17.4 CAPT GRADING SYSTEM

### 17.4.1 General Grading Rules

Lesions occupying more than one subfield are coded as present in each subfield and the area involved is estimated in each subfield separately. For drusen size, a drusen straddling one or more boundaries between subfields is considered only in the subfield where the largest part of it is located. If a drusen is split equally between two subfields, it is considered only in one subfield, the first in order on the form. When a grading decision for drusen size, area, confluence, or type is borderline, and either of two adjacent steps on the grading scale is considered valid, the smaller step is chosen.

**Questionable** - If the reader thinks that the lesion is probably absent, or is less than 80% certain the lesion is real, the code is questionable. If the reader is at least 80% certain that the lesion is present, a code indicating definite presence is assigned. When an abnormality is definitely present, but its nature is uncertain, the reader assigns the code of questionable for the lesion considered to be most likely and absent for the lesion(s) considered less likely.

**Cannot grade** - If a specific lesion can be seen in any part of the subfield it should be graded as such, even if the remainder of the subfield is upgradeable. If a lesion is not seen in a subfield, and greater than or equal to 75% of the subfield is obscured, either by a retinal or vitreal lesion or poor photo quality, cannot grade is chosen, rather than none.

**Cannot determine** - If a specific lesion can be seen but is not quantifiable from the fundus photograph.

### 17.4.2 Initial Visit Evaluations

The initial visit photographs are evaluated to determine the eligibility of the patient, as well as to provide a detailed description of the drusen characteristics.

The photographs taken immediately after treatment are evaluated for complications as a result of treatment and to monitor for deviations from the treatment protocol.

#### 17.4.2.1 Initial Visit Eligibility Evaluation

The Reading Center determines final eligibility for patients enrolled in CAPT (CAPT Baseline Eligibility Evaluation Form). The determination is made from the evaluation of an initial visit fluorescein angiogram and color stereo macular photographs. The patient's identifying information, date of photographs and quality of photographs are recorded. The Reading Center Director or the Principal Investigator will confirm all eligibility determinations.

The eligibility review confirms that 10 or more drusen ( $>125\ \mu\text{m}$ ) within  $3000\ \mu\text{m}$  of the foveal center are present in each eye. Serous pigment epithelial detachments, geographic atrophy within  $500\ \mu\text{m}$  of the foveal avascular zone, geographic atrophy  $>1$  MPS disc area, evidence of CNV, or any other ocular disease affecting vision disqualify the patient. If a condition is present that does not affect eligibility, then it is recorded under "other condition".

### 17.4.2.2 Initial Treatment Evaluations

Post-treatment stereoscopic color and stereoscopic red-free color fundus photographs of the macula are taken the same day as treatment. These photographs are received and graded by the Reading Center with respect to the number of visible burns within 3000  $\mu$  of the foveal center, and their intensity compared the with treatment standard, CAPT Treatment Intensity Standard photograph. In addition, immediate treatment complications are also noted, including choroidal hemorrhage and retinal hemorrhage.

### 17.4.2.3 Initial Visit AMD Characteristics

#### A. Drusen Presence and Size

The characteristics to be assessed in each subfield are the number of drusen greater than 63 $\mu$ m and the size of the largest drusen present. Although the presence of 10 or more drusen greater than 125 $\mu$ m is required in each eye for a patient to be eligible, drusen >63 $\mu$ m are considered for grading purposes in keeping with other studies recording drusen characteristics.

#### A.1 Large Drusen: Soft Distinct, Soft Indistinct and Reticular

Drusen larger than circle C-0 (> 63  $\mu$ ) typically are yellow-white in color and often have visible thickness. These are large drusen. Some have sharp margins and a nodular appearance (soft-distinct drusen, for example, those near the inner edge of the outer temporal subfield of **Wisconsin Standard Photograph #6**, and the majority of drusen seen in all subfields in **Wisconsin Standard Photograph #5**. Others have indistinct margins and a softer, less solid appearance (soft-indistinct drusen, for example, the large drusen at the center of **Wisconsin Standard Photograph #13** and the two above it).

The term "reticular drusen" has been chosen for the yellowish material that looks like flat soft drusen arranged in subtle to distinct networks of broad interlacing ribbons. An example of reticular drusen is visible in **Wisconsin Standard Photograph #10** in the outer superior and temporal subfields on either side of the 1:30 meridian.

When serial photographs of the same eye are examined, drusen can sometimes be seen to lose their substance and fade towards the appearance of diffuse RPE depigmentation, or to disappear entirely. When photos of a single visit are evaluated, it is difficult to know whether large drusen that appear flat or only slightly elevated, such as those in the outer superior subfield of **Wisconsin Standard Photograph #12**, are fading from a previous thicker stage. Drusen are graded as present if they are felt to maintain any of their substance.

#### A.2 Drusen Versus RPE Depigmentation

When drusen appear regressed from a thicker stage, but some substance remains, they are still considered to be drusen. If the edges are well defined the drusen is graded as soft distinct; if the edges are poorly defined they are classified as soft indistinct. When only a faint grayish haze remains or when the RPE appears diffusely involved, the lesion is RPE depigmentation.

In **Wisconsin Standard Photograph #6**, along with small drusen in all subfields and moderately large yellow-white soft-distinct drusen in most, there are some drusen that appear to have regressed and some that have reached the RPE depigmentation stage (central subfield and inner superior and temporal subfields). In the inner temporal subfield of **Wisconsin Standard Photograph #6** there are two patches of RPE depigmentation, a faint one in the superior part of the subfield extending across the 10:30 meridian, occupying an equally large part of the inner superior subfield, and another faint one inferiorly touching the 7:30 meridian in the shape of the top 1/3 of a pumpkin, with its stem curving in to touch the inner circle.

### **A.3 Estimating Size of a Single Druse Versus Confluent Drusen**

The margins of individual drusen are frequently indistinct when drusen are confluent. It may be difficult, therefore, to distinguish a confluent clump of small drusen from one large druse, and to determine the size of the drusen making up a confluent patch. When an area of drusen has regular borders, is not more than twice as long-as it is wide, and no single druse can be distinguished within the area, it is graded as a single large drusen. If, however, within such an area the borders of individual drusen can be distinguished for greater than or equal to 180 degrees with 90% certainty, the smaller of the two principal diameters of the largest druse present within the irregular patch is considered in estimating drusen size.

### **A.4 Estimating Largest Drusen in Each Subfield**

The reader is asked to record the size of the largest druse present in each subfield. No distinction is made between hard or soft drusen. Drusen are classified according to diameter. It is assumed that all drusen are round or oval in shape and that a single druse is no more than twice as long as it is wide. If a druse is oval, its shorter diameter is used to classify its size. Standard circles C-0, C-1 and/or C-2 are superimposed over or placed next to the largest druse in the subfield. If the shorter diameter of the druse equals or exceeds the diameter of the circle, the druse is judged to be equal to or greater than this circle in size. In using the circles, judge from the center of the line. The steps in the scale are as follows:

- None
- One or more drusen  $\geq$  the diameter of circle C-0, but all  $<$  the diameter of circle C-1 (125 $\mu$ m)
- One or more drusen  $\geq$  the diameter of circle C-1, but all  $<$  the diameter of circle C-2 (250 $\mu$ m)
- At least one drusen  $\geq$  the diameter of circle C-2
- Cannot determine
- Cannot grade



### A.5 Drusen Area

The area covered by drusen within each subfield is estimated by mentally moving together all drusen as if they were confluent and comparing this area to the areas of the standard circles (central, inner and outer). The grading scale is as follows:

- Not applicable
- Area < 10%
- Area 10% - < 25%
- Area 25% - < 50%
- Area 50% - < 75%
- Area  $\geq$  75%
- Cannot determine
- Cannot grade

In **Wisconsin Standard Photograph #1** the central subfield has no more than questionable drusen and area, therefore, is not assessed; in the remaining subfields the area is clearly less than 10%. **Wisconsin Standard Photograph #10** shows clear-cut reticular drusen in the outer superior, temporal, and inferior subfields, with extension into the inner superior and temporal subfields and outside the grid superiorly, temporally and inferiorly as well. In the outer temporal and inferior subfields, and in the inner superior subfield, reticular drusen clearly cover greater than or equal to 50% of the subfield. In the temporal half of the outer superior subfield reticular drusen are clear-cut and cover more than 50% of the retinal area. In the nasal half of this subfield the appearance is not so obviously that of reticular drusen, but it seems best to interpret the irregular pale areas here as reticular drusen as well.

### A.6 Drusen Confluence

Drusen confluence is defined as any touching or merging of two or more drusen. It is sometimes difficult to decide whether an oval-looking spot is a single druse or two (or more) smaller drusen partially merged. When in doubt, consider such lesions to be a single large druse, unless the longest diameter (length) is more than twice the width. In these cases, divide the lesions into component parts so that the length of each is no more than twice its width. Confluence is graded in each subfield according to the percent of total drusen area involved, but only if drusen size is greater than 63  $\mu\text{m}$  in that subfield.

The reader scans the field for a pattern of confluence. It should be emphasized that while confluence is graded subfield by subfield, the field should be scanned for a pattern of confluence before each subfield is graded. The codes and definitions are as follows:

- No area of confluence
- Questionable or < 10 pairs

- $\geq 10$  pairs
- Cannot determine
- Cannot grade

Most of the subfields in **Wisconsin Standard Photograph #1** contain discrete, non-merging drusen. In **Wisconsin Standard Photograph #4**, there are many examples of drusen confluence. Reticular drusen, by definition in this grading system, are confluent. When present in a subfield, reticular drusen are added to other confluent drusen when judging the total percent of confluence.

#### **A.7 Predominant Drusen Size in Field 2**

In eyes with drusen of differing sizes, recording only the largest drusen in each subfield may not characterize the predominant drusen size. Predominant drusen size is the most common drusen size present, regardless of area covered. It is recorded for the entire area within 3000  $\mu$  of the foveal center, using circles C-0, C-1 and C-2.

- Not applicable
- $< C-1$
- $< C-2$  but  $\geq C-1$
- $\geq C-2$
- Cannot determine
- Cannot grade

#### **A.8 Global Drusen Area**

Global drusen area is defined as the total area covered by drusen within the grid (total area in all subfields). The area covered by drusen within each subfield is estimated by mentally moving together all drusen as if they were confluent and comparing this area to the areas of the standard circles (central, inner and outer circles). The grading scale is as follows:

- Not applicable
- Area  $< 10\%$
- Area  $10\% - < 25\%$
- Area  $25\% - < 50\%$
- Area  $50\% - < 75\%$
- Area  $\geq 75\%$
- Cannot determine
- Cannot grade

## A.9 Reticular Pseudodrusen

The grading scale for reticular drusen (as described in section A.1) within 3000 $\mu$  of the foveal center is as follows:

- None
- Any
- Cannot determine
- Cannot grade

## B. Other Characteristics of AMD

### B.1 Focal Hyperpigmentation

Disturbances of the RPE sometimes lead to deposition of granules or clumps of gray or black pigment in or beneath the retina. Such pigment deposits are found in some eyes with age-related maculopathy, but may also be a result of previous traumatic, inflammatory, toxic, or congenital processes. Peripapillary pigment deposits are excluded from consideration. If the pathology is present but cannot be quantified, then a "cannot determine" is recorded. If the photographic quality does not permit grading of pigment deposits in a subfield, a "cannot grade" is recorded.

Circle C-2 is used in all subfields to estimate extent of pigment deposits associated with age-related maculopathy. All pigment deposits in a given subfield are mentally moved together and the area they would cover is compared with C-1. The grading scale is as follows:

- No pigment deposits
- Questionable pigment deposits
- Area of pigment < Circle C-2
- Area of pigment  $\geq$  Circle C-2
- Cannot determine
- Cannot grade

For **Wisconsin Standard Photographs #1 and #4**, all the subfields are graded "none". All subfields of **Wisconsin Standard Photograph #2**, with the possible exception of the inner inferior, are also graded "none", since the pigment present is RPE mottling. In **Wisconsin Standard Photograph #5** in the central subfield at 11:00 touching the edge of the large druse is a gray spot, which also should be graded no more than questionable. Definite focal hyperpigmentation, however, can be seen in the inner superior subfield. The total area covered by pigment is greater than C-1. Focal hyperpigmentation can also be seen under the venule crossing at the 1:30 meridian in the inner nasal subfield. This pigment should be graded greater than C-1. The total area of the focal hyperpigmentation in the inner circle is > C-2.

## B.2 Geographic Atrophy

Geographic atrophy is one or more sharply defined, more or less circular patches of partial or complete depigmentation of the RPE, which typically exposes choroidal blood vessels. To be classified as geographic atrophy, a patch must be greater than or equal to circle C-2 in total size to be considered definitely present (not necessarily all in the same subfield).

For a lesion to be graded as geographic atrophy, at least two of the three characteristics found in typical geographic atrophy are required: choroidal vessels visible, sharp edges, more or less circular shape. Increased visibility of the choroidal vessels is the single most important criterion, however, occasionally one may see a circular lesion with sharp edges and much of the RPE, though depigmented, still intact. Even though choroidal vessel visibility is not substantially different from that seen through normal RPE, this lesion could still be classified as geographic atrophy. Sometimes observing the eye without the viewer can aid in this determination; seeing a circular area with sharp edges enclosing an area wherein the RPE is clearly depigmented may tip the grading judgment from RPE depigmentation to geographic atrophy. The criterion of edge sharpness may be filled in either of two ways: 1) when the depigmentation within the patch is subtle, the edge must be abrupt and smooth, like one made with a cookie cutter, or 2) when contrast between depigmentation within a patch and the normal pigmentation around it is strong, the edge may be considered definite enough for this lesion even if the transition occurs gradually or irregularly over a zone up to 250 microns in width. Again, observing without a viewer may help in making this determination. If the pathology is present but cannot be quantified, then a "cannot determine" is recorded. The codes are defined as follows:

- Absent
- Questionable
- < 250 $\mu$
- Area  $\geq$  250 $\mu$  - < 1 MPS Disc Area (at least 250 $\mu$ m in width)
- Area  $\geq$  1 - < 2 MPS Disc Areas
- Area  $\geq$  2 MPS Disc Areas
- Cannot determine
- Cannot grade

Size is determined as the sum of all areas of GA.

A good example of geographic atrophy is shown in Standard Photograph #18. The central subfield and two-thirds or more of all inner subfields are involved. Note the sharp delineation where non-atrophic RPE meets the atrophic area. Large choroidal vessels are visible in the atrophic area. An example of questionable geographic atrophy is seen in Standard Photograph #8. The area of the questionable geographic atrophy falls within the inner nasal and inner inferior subfields.

### 17.4.3 FV 06 Evaluation

Color stereoscopic photographs of the macula of each eye are taken at 6 months. The photographs are evaluated for suspected exudation, geographic atrophy (GA), and drusen reduction.

Since there is no angiogram at 6 months, if there are signs on the color photographs such as hemorrhage, lipid, or a serous detachment of the sensory retina that indicate the possibility of CNV, the clinical center is notified. See the section on Exudative Events at the end of this chapter.

The quantity of GA in the eye is evaluated for the endpoint criteria of 1 DA of new GA since initial visit. When GA is present, the total area of all GA within 3000  $\mu$  of the foveal center is compared to GA present on the initial visit photographs. If this total area of GA has increased by 1 DA, the answer is "Yes". When there is less than 1 DA of new GA, the answer is No. Treatment scars that have become atrophic and meet the criteria for GA are included in the measurement of the total area of GA.

The 6 months photographs are compared to the initial visit photographs to determine if there is a reduction in the total area of drusen by 50% or  $\geq 50\%$  in each eye.

### 17.4.4 12 Month Evaluation

#### 17.4.4.1 Eligibility for Treatment at 12 Months

The participating ophthalmologist at each clinical center determines the eligibility of the patient for treatment at 12 months. If the ophthalmologist believes that the amount of drusen is on the border of the eligibility criteria for treatment, the decision should be made to treat. The Reading Center does not determine the eligibility for treatment at 12 months prior to the treatment.

The 12-month color photographs and fluorescein angiogram of each eye are evaluated to confirm eligibility for additional laser treatment at twelve months. The reader is masked as to which eye was initially treated or treated again at 12 months. An eye is eligible for additional treatment when there are 10 or more large drusen ( $>125\mu$ ) or an equivalent area within 1500 $\mu$  of the foveal center. Eyes are not eligible for treatment at 12 months when the patient was determined to be ineligible at the initial visit because of basal laminar drusen, pathologic myopia or pattern dystrophy. Eyes are not eligible for treatment at 12 months when CNV (classic, occult or mixed) or a serous PED of any size was identified at the initial visit or develops before or at the 12-month visit in either eye. An eye with geographic atrophy within 500 $\mu$  of the foveal center or geographic atrophy  $\geq 1$  MPS disc area in size at initial visit is not eligible for treatment. Likewise, if geographic atrophy develops before or at the 12 month visit within 500 $\mu$  from the foveal center or the total area of new geographic atrophy is  $\geq 1$  MPS disc area, the eye is not eligible for treatment.

If the Reading Center's interpretation of the photographs is that the eye met the criteria for additional treatment and the eye was not treated, a letter is sent to the ophthalmologist requesting that the patient be recalled and treated within 15 months of the initial visit.

#### **17.4.4.2 12 Month Treatment Evaluation**

When laser treatment is performed at the 12 month follow-up visit, the clinical center is directed to take post-treatment color and red-free color photographs that same day. These photographs are received and graded by the Reading Center with respect to the number of visible burns, their location, and their intensity compared with the CAPT Treatment Intensity standard.

In addition, immediate treatment complications such as choroidal hemorrhage or retinal hemorrhage are also noted.

#### **17.4.4.3 12 Month & Annual Evaluation of AMD Characteristics**

A modified version of the initial visit evaluation is performed at 12 months, and annually thereafter. Color stereoscopic photographs of the macula of both eyes and an angiogram with the early phase of both eyes are taken at 12 months and annually. The photographs are evaluated for changes in AMD characteristics, and to monitor for exudation and adverse events.

The photographs and angiogram are evaluated for the presence of exudation. If present, a detailed grading of the eye with exudation is performed (see 17.3.5 Exudative Event evaluation).

Geographic Atrophy is described in the 3 subfields (central, inner, and outer circles) in order to identify new areas of GA and the amount of new GA recorded in disc areas.

Drusen are evaluated for the number  $>125\mu$  in the three subfields, and recorded as  $< 10$ ,  $10-20$ , and  $>20$ . Drusen  $>63\mu$  are evaluated in each subfield compared to the initial visit, and recorded as same, more, or less, as well as for all subfields combined. Individual drusen are compared to the initial visit to determine if there has been a 50% reduction since the initial visit. As on the initial visit, the percent global area covered by drusen is recorded.

Any new condition since baseline is recorded.

#### **17.4.5 Exudative Event Evaluation**

If at any time during the study an investigator believes that a study eye, treated or observed, has developed exudation (CNV or PED), then the clinical center is directed to obtain color fundus photographs and a fluorescein angiogram. If an investigator is uncertain as to whether an event has occurred, then he/she may send these photographs to the Reading Center for a screening evaluation. The physician manages the patient at the clinical center at that time.

If at any time during the study, the Reading Center believes that a study eye, treated or observed, has developed exudation, then the clinical center is notified. A fluorescein angiogram is obtained and submitted to the Reading Center. The Reading Center reader then evaluates the fluorescein angiogram for leakage consistent with exudation. If present, an Exudation Event Grading Form is completed which characterizes the lesion according to its composition (classic CNV, occult CNV, serous PED), its location in relationship to the foveal avascular zone, its delineation (well defined or poorly defined borders), as well as its size in disc areas. The participating ophthalmologist determines the management of the patient. If the CNV is treated no additional photographs following treatment are obtained.

Examples of color fundus photograph appearances of RPE detachments either serous or associated with CNV are present in Standard Photographs #11, #12, and #16. Fluorescein angiographic criteria for CNV include late leakage of fluorescein dye beneath the retina and / or the retinal pigment epithelium. Purely serous RPE detachments have a well-delineated homogeneous pattern of fluorescence while fibrovascular RPE detachments are characterized by irregular elevation and fluorescein leakage at the level of the retinal pigment epithelium.

Any patient developing exudation continues to be followed in the study. Color stereo photographs and fluorescein angiograms are required at annual visits. When an eye receives treatment for CNV at any time during the study, post-treatment photographs are not required.

The Reading Center Director and the Principal Investigator review all cases of exudation. This information is recorded for reports for the Coordinating Center, Principal Investigator, Data and Safety Monitoring Committee, as well as for the CAPT Study meetings.

#### **17.4.5.1 Follow-up Evaluation of Exudative Events**

The evaluation of eyes with exudative events will include size, location, and type of CNV present (classic or occult). The eyes will be monitored to record when exudation is no longer actively leaking.

## CHAPTER 18

### COORDINATING CENTER OPERATIONS AND PROCEDURES

#### 18.1. RESPONSIBILITIES OF THE COORDINATING CENTER

To facilitate discussion, the responsibilities of the CAPT Coordinating Center are organized according to phase of the clinical trial. The phases are categorized as initial design and protocol development, final preparation for trial initiation, patient recruitment, patient treatment and follow-up, patient closeout, and final termination of the trials.

##### 18.1.1. Initial Design Phase and Protocol Development

During the initial design phase of CAPT, Coordinating Center staff, played a major role in the following activities:

- Developing the study design, including sample size calculations;
- Outlining the data collection schedule;
- Outlining plans for data analysis;
- Outlining data processing procedures;
- Drafting most chapters of the *Manual of Procedures*;
- Drafting the data collection forms;
- Initial testing and refining of the data collection forms and procedures during the pilot study;
- Initial testing and refining of the data processing procedures used during the pilot study;
- Developing procedures for training and certifying staff at the clinical centers during the pilot study;
- Preparing other materials to be used by clinical center staff, such as patient logs and other auxiliary forms;
- Developing quality assurance procedures for all aspects of the CAPT.

##### 18.1.2. Final Preparation for the Initiation of the Trial

Prior to initiating CAPT, a number of activities were performed by the staff of the Coordinating Center to begin the trial with a fully developed protocol and well trained staff for all aspects of CAPT. These activities included:

- Finalization of the protocol details;
- Fine tuning the data collection and data management system to integrate all CAPT activities including photograph grading data;



- Development of computer systems to automatically generate appointment schedules and labels for photographs and data collection forms at the time of randomization;
- Training staff at the CAPT clinical centers;
- Training and certifying visual function examiners;
- Distributing the *Manual of Procedures* to all clinical centers;
- Supplying each clinical center with a set of CAPT data collection form masters;
- Generating treatment allocation schedules for automated and manual backup randomized assignment;
- Preparing and distributing minutes of meetings;
- Establishing a repository for CAPT data and other CAPT documents, such as minutes, manuals, etc.;
- Ensuring that each clinical center has the required equipment, charts, and facilities;
- Holding a meeting of the Data and Safety Monitoring Committee to review the protocol;
- Finalizing procedures for site visits to clinical centers;
- Collaborating with the Reading Center to refine the editing of grading forms;
- Collaborating with the Reading Center to finalize the quality control program for photo grading;
- Drafting a CAPT patient brochure, referring physician brochure, newsletter to clinical center staff, and standard slides for training and presentations to enhance recruitment.

### **18.1.3. Patient Recruitment and Treatment and Follow-up Phase**

Activities during this phase can generally be categorized as administrative, data collection and processing, data analysis and reporting, quality assurance, and planning for future phases. Coordinating Center responsibilities are summarized for each category.

#### *Study Administration*

- Participating in the affairs of each of the standing committees;
- Coordinating and providing the necessary logistical support for all CAPT meetings;
- Coordinating communications among the various CAPT centers and committees;
- Assisting the staff of each clinical center to interpret and follow the protocol and procedures documented in the *Manual of Procedures*;
- Supplying the clinical centers with new and revised data collection forms and other printed materials;

- Maintaining accurate study archives, including study history and proceedings of committee meetings;
- Issuing random assignment designating the eye of the patient assigned to treatment;
- Preparing appointment schedules for the clinical centers to alert staff to dates on which clinic visits are expected;
- Preparing and distributing to clinical centers reminders of upcoming patient visits, patients to be contacted by telephone, and materials overdue at the Coordinating Center;
- Preparing and distributing to clinical centers patient labels to assist coordinators in properly labeling forms and photographic materials sent to the Coordinating Center and Reading Center.
- Preparing lists of the patients requiring telephone administration of the quality of life assessments;
- Notifying the Reading Center of the photographs expected;
- Maintaining an accurate CAPT telephone, address, fax, and e-mail directory.
- Publishing and distributing CAPT study newsletters for patients and clinical center staff.

#### *Data Collection and Processing*

- Receiving completed data collection forms from the clinical centers;
- Entering the data into an electronic database;
- Storing the data for computer processing;
- Maintaining an inventory of all data forms received at the Coordinating Center;
- Maintaining an inventory of all data records created by the graders at the Center;
- Editing the data for completeness, accuracy, and consistency and resolving questionable information with the Clinic Coordinators;
- Correcting data files in response to queries resolved by clinic and Reading Center staff.
- Performing the telephone administered QOL interviews;

#### *Data Analysis and Reporting*

- Preparing reports for the Investigative Group concerning the status of patient recruitment and follow-up, adherence to the protocol, quality of data collected, and clinic response to queries;
- Preparing periodic reports for the Data and Safety Monitoring Committee concerning adverse and beneficial treatment effects;

- Developing analytic methods and methods of data collection appropriate to the CAPT design, in conjunction with the Data and Safety Monitoring Committee;
- Preparing all analyses to be reported in publications from CAPT;
- Participating in the drafting of all CAPT publications;
- Performing other analyses deemed appropriate by the Executive Committee, Data and Safety Monitoring Committee, or other Study participants as time permits;
- Monitoring the accumulating data to determine whether the assumptions used to calculate sample size requirements are met and recommending modifications to the CAPT design if these appear to be necessary;
- Reporting to appropriate audiences statistical and methodological innovations developed during the course of the CAPT.

#### *Quality Assurance*

- Conducting initial training sessions for clinic personnel to review study design, data collection methods, and procedures for interfacing with the Coordinating Center and Reading Center;
- Visiting each clinical center on a regular basis to review procedures and to "troubleshoot";
- Preparing monthly reports summarizing patient recruitment in each center,
- Preparing quarterly reports on adherence to protocol in the clinical centers;
- Maintaining documentation of all procedures and operations at the Coordinating Center;
- Maintaining the data files in a secure manner to assure their integrity;
- Backing up the data files to assure that data are not lost;
- Reporting periodically on the quality of the data accumulated at the Coordinating Center,
- Reporting on the quality of data processing operations at the Coordinating Center,
- Cooperating with any individual or group assigned to review operations at the Coordinating Center.

#### *Planning for Future Phases*

- Developing procedures for closing out patient follow-up at the appropriate time;
- Planning for permanent, accessible storage of CAPT records and data.

#### **18.1.4. Patient Closeout Phase**

As with earlier phases of CAPT studies, during the Patient Closeout phase the primary responsibilities of the Coordinating Center staff are concerned with coordination, developing, testing, and refining procedures, and data processing and analysis. Specific responsibilities during this period are:

- Familiarizing clinic staff with closeout procedures;
- Coordinating patient closeout;
- Monitoring adherence to established procedures for patient closeout;
- Developing plans for final data editing and storage;
- Completing plans for final analysis and preparation of publications;
- Developing plans for final disposition of the data files;
- Participating in paper writing activities;
- Providing a mechanism for continuing communications among investigators and performing additional analyses.

#### **18.1.5. Termination Phase**

During the last phase of the CAPT during which funding is available, the Coordinating Center may be the only center funded. However, during this period communications with the investigators at the clinical centers will be important. The following activities are those anticipated for the Coordinating Center during this period:

- Completing scheduled data analyses;
- Placing data files and other materials in the selected archives;
- Distributing draft manuscripts and reprints of publications to the other investigators;
- Serving as the communications center.

### **18.2. ORGANIZATION OF THE COORDINATING CENTER**

#### **18.2.1. Internal Organization**

Staffing may change as CAPT progresses. The staffing of the Coordinating Center includes the following roles (see Exhibit 18-1):

- Director/Senior Biostatistician
- Project Director
- Protocol Monitor/Research Associate
- Systems Analyst

- Junior Biostatistician
- Programmer
- Administrative Assistant
- Data Coordinator

The Director leads the general scientific and administrative affairs of the Coordinating Center and the data analytic responsibilities in particular. The Project Director will have primary responsibility for the overall quality assurance program, will oversee the activities related to preparing for CAPT committee and group meeting, and will manage many of the day-to-day activities of the Coordinating Center.

### **18.2.2. Personnel Responsibilities**

The Director has responsibility for providing leadership and guidance to CAPT in areas related to study design, administration, and implementation. The Director also has overall responsibility for all functions of the Coordinating Center and works closely with the Project Director to determine the general approach and methods to be used in each area of operation of the Coordinating Center. Specific responsibilities include:

- To serve as a voting member of the CAPT Operations Committee with responsibility for developing the agenda for each meeting;
- To serve as a voting member of the CAPT Executive Committee with responsibility for developing the agenda for each meeting in consultation with the CAPT chair;
- To lead the organization and planning for meetings for the Investigative Group;
- To serve as a non-voting member of the Data and Safety Monitoring Committee;
- To lead internal meetings of the Coordinating Center staff;
- To provide advice and guidance to the Project Director, Systems Analyst, Junior Biostatistician, Research Associate, and Administrative Assistant on methods consistent with the standards of good practice for multi-center clinical trials.

The Director in the role of Senior Biostatistician works closely with the Systems Analyst to oversee all aspects of data control, data entry, data management, and data reporting. Specific responsibilities in this role include:

- To develop new data collection forms, in consultation with other Coordinating Center staff;
- To consult with the Systems Analyst in the refinement of the data management system and development of new subsystems;
- To assist with planning and preparation of Data and Safety Monitoring Reports;
- To serve as a resource in problem solving for the clinical centers and Reading Center;

- To develop analyses of the data required for adequate monitoring of all aspects of treatment benefit or harm;
- To develop analyses to detect outlier data and data patterns that may indicate irregularities in data collection procedures;
- To develop new statistical methodology as indicated and to present and publish such methodology appropriately;
- To collaborate with the other Study investigators to prepare CAPT findings for publication;
- To work with the Project Director on quality assurance activities at the Coordinating Center, Reading Center, and clinical centers.

The Project Director has a pivotal role in the Coordinating Center as the supervisor of overall quality assurance activities and coordinating center activities. She also will oversee administration of the quality of life instruments. Specific responsibilities include:

- To have a thorough knowledge of the CAPT protocol and the rationale behind the key design points, as well as knowledge of the key principles of clinical trials design and practice;
- To serve as a voting member of the CAPT Operations Committee;
- To serve as a voting member on the CAPT Executive Committee;
- To serve as chair of the CAPT Clinic Monitoring Committee;
- To supervise quality assurance activities at the Coordinating Center and clinical centers with input from the Director;
- To provide telephone support to clinical center staff with questions regarding the CAPT protocol (with the exception of questions on visual function, which should be directed to the Research Associate) and to refer appropriate questions to the Director of the Coordinating Center, the Director of the Reading Center, or the CAPT Study Chair;
- To supervise the day-to-day Coordinating Center activities in the areas of data collection, data processing, data reporting, data analysis, quality assurance and administrative support activities;
- To develop, in association with the Director, the Coordinating Center budget for annual continuation applications;
- To perform some of site visits to the clinical centers and write summary reports;
- To maintain a Log of Extraordinary Events for exceptional circumstances and significant deviations from the protocol;
- To continually review and update the *CAPT Manual of Procedures*
- To critically review all interim reports for consistency and accuracy;

- To supervise the production of the periodic reports required by the CAPT Data and Safety Monitoring Committee, Investigative Group, and Clinic Monitoring Committee;
- In conjunction with the Research Associate and Administrative Assistant, to review eligibility and exclusion criteria for each Study candidate before issuing a random allocation;
- To expand and refine the documented procedures for administration of the NEI-VFQ;
- To plan and present the initial training for all Clinic Coordinators;
- To review the accumulating data from the quality of life instruments for indicators of performance and in the context of the information on visual function for interim and final reports;
- To oversee the production of the CAPT newsletters for patients and clinic staff;
- To collaborate with other CAPT investigators to prepare CAPT findings for publication.
- To act as director of the Coordinating Center in the absence of the Director;

The Research Associate will be the first line contact with clinical center staff with regard to issues of certification and visual function examination. Specific responsibilities include:

- To keep in touch with the staff of each of the clinical centers through regularly scheduled telephone interviews with each Clinic Coordinator quarterly and to bring areas of concern to the attention of the Project Director and/or Clinic Monitoring Committee;
- To provide telephone support to clinical center staff with questions regarding the CAPT protocol on visual function and to refer appropriate questions to the Director or Project Director of the Coordinating Center;
- To maintain the database on CAPT certified personnel;
- To follow-up on identified problems until they are resolved;
- In conjunction with the Project Director and Administrative Assistant, to review eligibility and exclusion criteria for each Study candidate before issuing a random allocation;
- To draft the CAPT patient information brochure and brochure for referring ophthalmologists;
- Perform telephone administration of the NEI VFQ-25 instrument at the Follow-up Visit at 60 months, as necessary;

The Administrative Assistant will be a resource on the handling of data collection documents and other study materials for the clinical centers and will provide secretarial and administrative support to the Coordinating Center. Specific responsibilities include:

- In conjunction with the Project Director and Research Associate, to review eligibility and exclusion criteria for each Study candidate before issuing a random allocation;
- To query clinical center staff about missing and delinquent forms;
- To prepare data collection forms and revised components;
- To maintain a history file of all revisions of all forms;
- To maintain an up-to-date telephone, address, FAX, and e-mail directory for the CAPT;
- To maintain the CAPT Coordinating Center Handbook of Policy and Procedures;
- To maintain a current version of the *Manual of Procedures* and distribute updates to all centers;
- To maintain a history file of all versions of the *Manual of Procedures*;
- To coordinate activities for staff recruitment with the university personnel office;
- To place orders for materials and track their status;
- To develop layout and final copy for special CAPT materials;
- To make travel arrangements for Coordinating Center personnel and for members of various CAPT committees;
- To oversee preparation and assembly of Study documents and reports;
- To maintain office supplies for the Coordinating Center,
- To maintain up-to-date records of cumulative Coordinating Center expenditures and unobligated funds;
- To assist the Principal Investigator and Project Director with budget preparation for annual continuation applications;
- To assist the Coordinating Center Director as necessary to meet the needs of the Study.
- To make arrangements for Study meetings, including contacting hotels, reserving rooms, identifying participants, and authorizing payment of bills.



Because the Coordinating Center serves as the data processing and analysis arm of the Study, data processing staff members are crucial to the successful operation of the Coordinating Center. Specific responsibilities of the Systems Analyst are:

- To develop and maintain a data processing system which meets the needs of CAPT;
- To prepare data reports for review by the Data and Safety Monitoring Committee at least once a each year;
- To advise the Director on data processing hardware, software, and personnel requirements;
- To do any necessary programming for data analysis under the supervision of the Director;
- To supervise other data processing staff;
- To act as "troubleshooter" for all computerized operations carried out by other members of the staff;
- To assure that adequate documentation of the data processing system is available at all times;
- To assure that adequate procedures have been established and maintained for preserving the integrity and security of the database;
- To advise the investigators on all activities that interface with the data processing system.

The Programmer and Data Coordinators are responsible for assisting the Systems Analyst with operation of and refinements to the data processing system. The Programmer's responsibilities include:

- Maintaining the data processing system;
- Maintaining the integrity of the database;
- Running database edit and update programs;
- Preparing and maintaining documentation of programs, procedures, and file structures;
- Generating randomization schedules for the randomized trials;
- Assisting with preparation of reports for review by the Data and Safety Monitoring Committee at least once a each year;
- Generating regular performance reports and reminders;
- Selecting information from the data files to be checked during clinic visits by the site visitors to the clinics;
- Assuring that sufficient backup is provided for all Study data files;
- Performing other data processing tasks as directed by the Systems Analyst and other Coordinating and Reading Center investigators.

Data Coordinators are responsible for managing the paper forms from the clinical centers and for providing the Administrative Assistant with help in clerical activities. Specific tasks are:

- To check all incoming materials against log sheets and notify coordinators of problems with materials sent;
- To log receipt of materials into a computer database;
- To enter all data into a computer database;
- To file all entered forms;
- To compare edit messages against original forms to detect data entry errors;
- To review computer-generated edit messages, i.e., queries regarding questionable data, and mail them to the appropriate centers;
- To generate, by executing a computer program, an appointment schedule and set of labels for each patient enrolled;
- To mail appointment reminders and notices to Clinic Coordinators each month;
- To photocopy forms, the *Manual of Procedures*, and other materials when requested;
- To type CAPT correspondence;
- To type agendas and other materials required for CAPT meetings;
- To format or type reports from clinic site visits;
- To type manuscripts;
- To print mailing labels for all CAPT personnel;
- To assist with preparation and assembly of reports;
- To type and distribute minutes of the meetings of the Data and Safety Monitoring Committee, Executive Committee, Clinic Monitoring Committee, and Coordinators' Group;
- To assist all Coordinating Center staff members as necessary to meet the needs of the Study.

The Junior Biostatistician will assist the Director, Project Director, and Director of the Reading Center in activities related to data analysis and interpretation with guidance from the Senior Biostatistician. Specific responsibilities include:

- To perform the analyses of inter-grader and intra-grader reliability of the assessments of CAPT color photographs and stereo angiograms;
- To develop, document, test and maintain statistical analysis programs for CAPT outcome data; in particular, linear and proportional hazards regression analysis for matched data;
- To assist the Systems Analyst and Programmer in incorporating appropriate statistical summary measures and tests in routine reports;
- To perform analyses of the CAPT data aimed at detection of outliers, data collection errors, and possibly fraudulent data collection;
- To support the implementation of the statistical stopping guidelines associated with interim data analyses as approved by the Data and Safety Monitoring Committee
- To support the needs of CAPT writing committees by preparing accurate and timely analyses of the data, as requested;
- To perform other data analytic tasks as directed by Director and other Coordinating and Reading Center investigators.

### **18.3. RANDOMIZED TREATMENT ALLOCATIONS**

The Coordinating Center is responsible for assigning which of the patient's eyes will receive the laser treatment. Four people at the Coordinating Center are authorized to issue random assignments: The Director, the Project Director, the Protocol Monitor and the Administrative Coordinator. Randomized assignments will be issued from the Coordinating Center during a telephone conversation between the Participating Ophthalmologist, Clinic Coordinator, and one of the authorized Coordinating Center "randomizers". The randomized assignment is given to the ophthalmologist, who verbally confirms the assignment. The Clinic Coordinator also repeats the assignment back to the Coordinating Center randomizer to verify accurate transmission of the assignment. Random treatment allocations will be computer generated and stratified by clinical center. A permuted block method of randomization will be used to assure balance over time and a random block size will be used to thwart any attempts to determine the next treatment allocation.

#### **18.3.1. Review of Eligibility and Random Assignment**

After a patient has been evaluated for CAPT in the clinical center and the ophthalmologist determines that the patient is eligible, the Clinic Coordinator is required to submit, via FAX, a completed Eligibility Checklist to the Coordinating Center (215-615-1531) and to arrange, via telephone, the anticipated time of randomization. Patients are required to be in the clinic and

prepared to have an eye treated at the time of study enrollment. The Clinic Coordinator telephones the Coordinating Center (215-615-1500) for an allocation specifying which eye will receive laser treatment and which eye will receive no treatment. The Clinic Coordinator gives the authorized randomizer on call the CAPT ID number, name code and clinic site. This information is used by the randomizer to initiate a CAPT Randomization Record. The Participating Ophthalmologist answers the questions on the ophthalmologic eligibility criteria to make a final check that all eligibility criteria have been met. Expanded definitions of certain items on the checklists are kept in a notebook for quick consultation if clarification is needed. If the proper complement of responses is recorded, the randomizer provides the next assignment on the randomization schedule for the clinical center. She relays the assignment to the enrolling ophthalmologist and requests that both the ophthalmologist and the coordinator verify verbally the correct assignment.

If the patient's eligibility cannot be ascertained, either the patient is not enrolled or the random allocation is delayed until one or more members of the Operations Committee can be consulted and an exception or clarification can be made. If it is necessary to consult the Operations Committee, this fact and the outcome are documented in the Log of Extraordinary Events maintained in the Coordinating Center by the Project Director.

### **18.3.3. Associated Clinic Aids**

Once a new patient has been enrolled, the Data Coordinator will enter the data to create a randomization record and invoke a computer program to generate a confirmation of assignment, an appointment schedule, labels for data collection forms, and a set of photograph labels. The confirmation will be faxed to the clinical center immediately and the schedule and labels will be sent out in the mail.

## **18.4. DATA CONTROL AND DATA PROCESSING**

The CAPT Coordinating Center Systems Analyst has designed and implemented a computer data system that facilitates the management and analysis of all CAPT data. In addition, the system aids with monitoring performance of CAPT Clinical Centers. All data processing is performed using an NT network file server linked with personal computers. Tapes are used for backup and recovery.

### **18.4.1. Initiation of Patient Records**

The CAPT data processing system (see Exhibit 18-2) begins for each patient with the randomization of a patient and the simultaneous creation of a record of key information about the patient in a master file. From that point on, all data from the clinics and the Reading Center are checked against the master files with regard to ID number and namecode before acceptance into the CAPT system.

### **18.4.2. Receipt and Initial Processing of Incoming Data**

Forms from clinical centers are received in the CAPT Coordinating Center via the U.S. Mail or whichever carrier clinical center staff chooses to use. Photographs and angiograms are similarly sent to the CAPT Reading Center. The Data Coordinator opens the mail and stamps all transmittal logs with the current date. Identifying information from the forms will be keyed to log receipt. A parallel system for receipt of materials exists in the CAPT Reading Center.

### **18.4.3. Design of Data Collection Forms**

The CAPT data collection forms were adopted with modification from the forms used in the pilot study, the CNVPT. The forms were designed to allow direct completion by the Clinic Coordinators, Visual Function Examiners, and Ophthalmologists during patient examination and to facilitate accurate data entry. The layout of the forms generally consists of two columns; the left column consisting of items required for all patients and the right column consisting of items that are answered conditional on the responses to the items in the left column. The correct logical flow is conveyed through use of directional arrows. Multiple choice and check-off responses are used as much as possible; however, unusual findings may be recorded in comment fields that are keyed in their entirety. Key instructions on additional actions to take or forms to complete are included in the form items.

Logical sections of the forms, such as patient history, refraction and visual acuity, quality of life questionnaire, etc., are divided into different form sections or components, with numbering of items specific to the component. The component concept allows for modularity of form design and therefore minimizes the impact of form revisions. Whenever appropriate, the same form components are used at the baseline examination and the follow-up examinations.

### **18.4.4 Data Entry**

Data entry, the transcription to computer files of written responses on CAPT paper forms, is performed using MS ACCESS, a database program. The Data Coordinators are responsible for data entry of CAPT transmittal logs and forms sent from clinics and the CAPT randomization record completed within the Coordinating Center. At the start of the data entry process, the Data Coordinator must indicate on the data entry screen the form date and version number associated with the form to insure proper entry.

The data entry forms on the computer screen appear as close to the paper form as possible. Checklists on the forms appear as checklists on the computer screen. Instead of typing names of clinic personnel, pull-down lists are used to select names. This insures better consistency of data. Data are checked online for validity of codes, values, and dates. The patient ID and name codes are checked against a master table to prevent invalid entry. Special codes may be entered for missing, illegible, or ambiguous data.

The Data Coordinators are instructed to check the entered data on each screen against the data on the form. This step is performed in lieu of a key verification phase that is often a part of associated data entry systems. CAPT data entry personnel are familiar with the CAPT protocol and have an understanding of the data that are being keyed. Evaluations by the Coordinating Center of the Macular Photocoagulation Study have demonstrated that "educated" data entry personnel using a data entry system with real time validity and range checking and extensive post-entry editing can provide very accurate (3 errors per 10,000 keystrokes) data entry. (Hosking, 1995) Despite the fact that CAPT data entry personnel are "educated", they are instructed to be objective and not to interpret ambiguous or illegible responses.

#### **18.4.5. Data Edit**

Entered data are read from the MS ACCESS files into SAS system files on a daily basis. For each form component there exists a corresponding component edit table for use by SAS that contains the specifications for consistency checking between items on a form component, across components within a form, and across forms for selected critical items. Paired with each check is a customized message that is printed when the conditions specified by the check are not met. This system provides a high degree of flexibility in specifying edit checks and edit messages. As with the data entry system, revisions and additions are made by modifying the appropriate edit table.

Edit messages generated by the system are sent to the originating center on a bi-weekly basis. When data items are involved in an edit "failure", those items are incorporated in a corresponding edit message (or a re-edit message if the component is being re-edited due to a correction). The message requests correction or confirmation, and is sent to the clinic or reading center. Before being forwarded for resolution, the edit messages are reviewed by the Data Coordinator. During this review, messages that were generated as a result of data entry error are identified and an error correction procedure is used to correct the data record. The corrected data record is re-edited.

#### **18.4.6. Edit Corrections**

When edit messages have been completed by the Clinic Coordinator with corrected or confirmed values, they are returned to the Coordinating Center. The Data Coordinator, again using MS ACCESS, enters the responses. The date and reason for the correction are recorded. Records involved in changes are again subjected to the editing system. The program that handles the entry of responses from edit messages and the correction of data entry errors as mentioned above creates a transaction record that contains sufficient identifying information (ID number, namecode, form component, visit, visit date, item number) and information regarding old and new values to construct a completely reproducible audit trail. When extraordinary circumstances arise in which the query may never be able to be resolved to meet the requirements of the edit logic, the Systems Analyst may, with the approval of the Project Director, flag specific items on specific forms as exempt from further edit.

#### **18.4.7. Backup of the CAPT Database**

The CAPT database, data management system, and data analysis system represent the efforts of the entire Investigative Group over the duration of the study. The main database resides on the file server and is backed up nightly. A rotation of backup tapes is maintained so that the database can be restored as of the most recent day, week, or month as well any past months. A copy of the monthly backup tapes is also stored off site. All CAPT Coordinating Center personnel are required to keep copies of key documents on the file server, which is on an automatic backup schedule. Files of the data system as of the time of each freeze and for each publication are also archived.

### **18.5. PREPARATION OF ROUTINE REPORTS**

The Coordinating Center provides reports based on available information to support the clinical centers, the quality assurance activities of the study (see Chapter 12), and the periodic meetings of the Operations Committee, Executive Committee, Investigative Group, and Data and Safety Monitoring Committee.

#### **18.5.1. Creation of Data Sets for Reporting**

Certain reports that are geared to check the completeness of activities in the clinical, reading, and coordinating centers are run on the current database, usually involving the master files and auxiliary files and programs that identify and count specific data collection forms or photographic gradings without analyzing the content of the data record. Other reports geared to a comprehensive summary of the study data require a significant amount of preparation and a data cutoff date must be chosen (usually the end of the month 30 to 60 days before the report is needed) so that the data files are not continually changing while work on the report is ongoing. When the cutoff date arrives, a "snapshot" of the data files is created. This process is often referred to as "freezing the data."

Before proceeding with the freeze, checks are run to verify the completeness of available information. Backlogs of data entry and grading of photographs are cleared. Normal day-to-day operations in the coordination area are delayed for only a day or so while the freeze and copy process takes place. The frozen copy of the data is then used as input to the numerous programs that perform the functions necessary to produce the tables for the report.

#### **18.5.2. Creation of Data Extracts**

The frozen datasets consist of the full complement of SAS system files that are updated daily from the MS ACCESS files used in data entry. Specific summary files are created that contain important data that will be used for many reports/tables such as visits completed, the visual acuity in study eyes at each study visit, or the time to event for the secondary outcome measures development of CNV, development of serous PED, or development of geographic atrophy.

### 18.5.3. Database of Tables

During the course of CAPT, hundreds of tables will be used for the various committee meetings. Some tables are used in reports to several committees. In order to keep generation of the tables efficient and organized, a database on the tables is maintained (here "table" is used loosely, and may refer to a formatted listing or graph). Each table is assigned a working number. Associated with each working number is a file containing the full name of the table, the person responsible for the generation of the table, the name of the computer programs that produce the data used within the table, the datasets required to be in existence before the program is run, and how the output is transformed into presentation quality (direct print output, reformatting through word processing routines, or typing). A paper file contains the latest hard copy version of the table, as well as the output supporting the table. The Project Director maintains a master list of working tables. For a particular report, the working tables may be put into any order.

### 18.6. OTHER DATA ANALYSIS

In addition to scheduled reports, the Coordinating Center staff members are responsible for performing all data analysis tasks. Such tasks may be associated with preparation of publications and presentations from the CAPT investigators, with funding renewals or initiatives, or with continuing data monitoring.

### 18.7. QUALITY ASSURANCE ACTIVITIES RELATED TO DATA MANAGEMENT

The overall quality assurance program in CAPT is described in Chapters 11 and 12. Specific quality assurance features related to data management are:

- Standard data collection forms and procedures;
- Central concurrent processing of data to detect problems early and provide feedback to the clinics, reading center, and interviewing organization;
- Data edits for missing, invalid, and suspect responses;
- Regular reporting on performance of all centers;
- Checking a 5% random sample of all entered data against original data collection forms after data editing has been completed. If this procedure identifies an unacceptably high residual error rate (more than 15 errors per 10,000 keystrokes) all aspects of data management will be reviewed with special attention to data entry procedures and staff;
- Explicit instructions with each distribution of new data collection form masters about new/revised questions and instructions to discard all previous versions and copies.



### 18.7.1 Quality Assurance Activities Related to Data Entry

The purpose of quality assurance related to data entry is to assess the accuracy of the system by which data from Coordinating Center forms are entered into the database. The residual error rate (errors in the database resulting from inaccurate data capture after the database records have undergone routine editing procedures) will be determined based on the keystrokes and fields checked. The nature of any discrepancies will be investigated to identify any systematic problems.

The process by which this activity will occur is listed below:

- On a monthly basis, the Systems Analyst draws a 5% random sample of forms that were entered into the database within a specific period of time, usually 1 month. All form types that were entered during that period are subject to selection. The content of the database for each form is printed out in a formatted manner.
- The Data Coordinators pull the selected forms from the files and attach the computer printout to the corresponding data collection form.
- The Project Director assigns the data checking team, which consists of all Coordinating Center staff except for data entry staff.
- If the form has one or more discrepancies that are considered an error, a notation of the discrepancy is made on the log and each page with a discrepancy is photocopied to document the discrepancy.
- Upon completion of the data checking, all data collection forms are returned to the data coordinators for re-filing. The Systems Analyst tabulates the total number of fields and keystrokes that were contained in the sample and the number of discrepancies in order to calculate the number of keystrokes in error per 10,000 keystrokes as well as the number of fields in error per 1,000 fields.
- These counts, the time period the forms were data entered, and the data entry operator(s) will be available for future tabulations to be reviewed by the CAPT Data and Safety Monitoring Committee.
- The Systems Analyst provides the Director and Project Director with the discrepancy counts as described above for each period, as they are performed.

### 18.8. PREPARATIONS FOR STUDY MEETINGS

A major factor in assuring good communications among Study personnel in the various centers and adherence to the protocol are the Investigative Group meetings held once each year. The Coordinating Center staff members play a major role in preparing for these meetings and providing logistical support for them. Similarly, Coordinating Center personnel also make arrangements for meetings of the Operations Committee, Executive Committee, Clinic Monitoring Committee, and Data and Safety Monitoring Committee.

The Administrative Assistant has major responsibility for arranging a meeting site and lodging. Reservations for these facilities are typically made 6 to 12 months in advance. Meeting locations are selected in consultation with the CAPT Chair and other members of the Executive Committee. A tentative schedule for the meeting is prepared in consultation with the Coordinating Center Director and Study Chairman so that sufficient meeting rooms are available when concurrent sessions are in progress.

Approximately two months before the meeting, a memorandum outlining the meeting schedule is sent to all Principal Investigators and Coordinators at the clinical centers. The memorandum also includes a request for a list of meeting participants. The responses to this mailing are used to refine estimated room requirements provided to the hotel. A list of participants is prepared for the meeting. This list is used by the Data Coordinators to prepare nametags.

The Study Chairman and the Coordinating Center Director prepare the meeting agendas in consultation with other members of the Coordinating Center and Reading Center staff. The agendas guide the assembly and preparation of materials to be discussed at the various meetings. Meeting notebooks are prepared to facilitate the discussions of the Executive Committee and Investigative Group.

Minutes of the meetings, oriented toward action items, are prepared and distributed by various members of the Coordinating Center staff, depending on the meeting. Copies of minutes are distributed to all members of the committee and filed in the CAPT Library maintained at the Coordinating Center.

## **18.9. STUDY LIBRARY**

The Coordinating Center is responsible for maintaining a record of study progress and activities. Responsibility for maintaining a Study Library has been assigned to the Administrative Assistant. The following documents are kept in the CAPT Library for reference by Coordinating Center staff and other study investigators:

- Minutes of meetings:
- Operations Committee
- Executive Committee
- Investigative Group
- Clinic Monitoring Committee
- Investigative Group Progress Reports
- Site visit reports
- Reports from quarterly telephone calls to Clinic Coordinators

- Previous and current versions of *Manual of Procedures*
- Copies of papers cited in the *Manual of Procedures*
- Copies of papers cited in study publications
- Published data
- Copies of reports from site visits to the Coordinating Center and Reading Center
- Protocol memoranda
- Archive of previously used versions of data collection and grading forms
- Log of Extraordinary Events
- Reprints of CAPT publications.

Other materials may be added to the Library as directed by the Coordinating Center Director. Copies of confidential data reports and meetings of the DSMC are kept in a locked filing cabinet in individual staff offices.

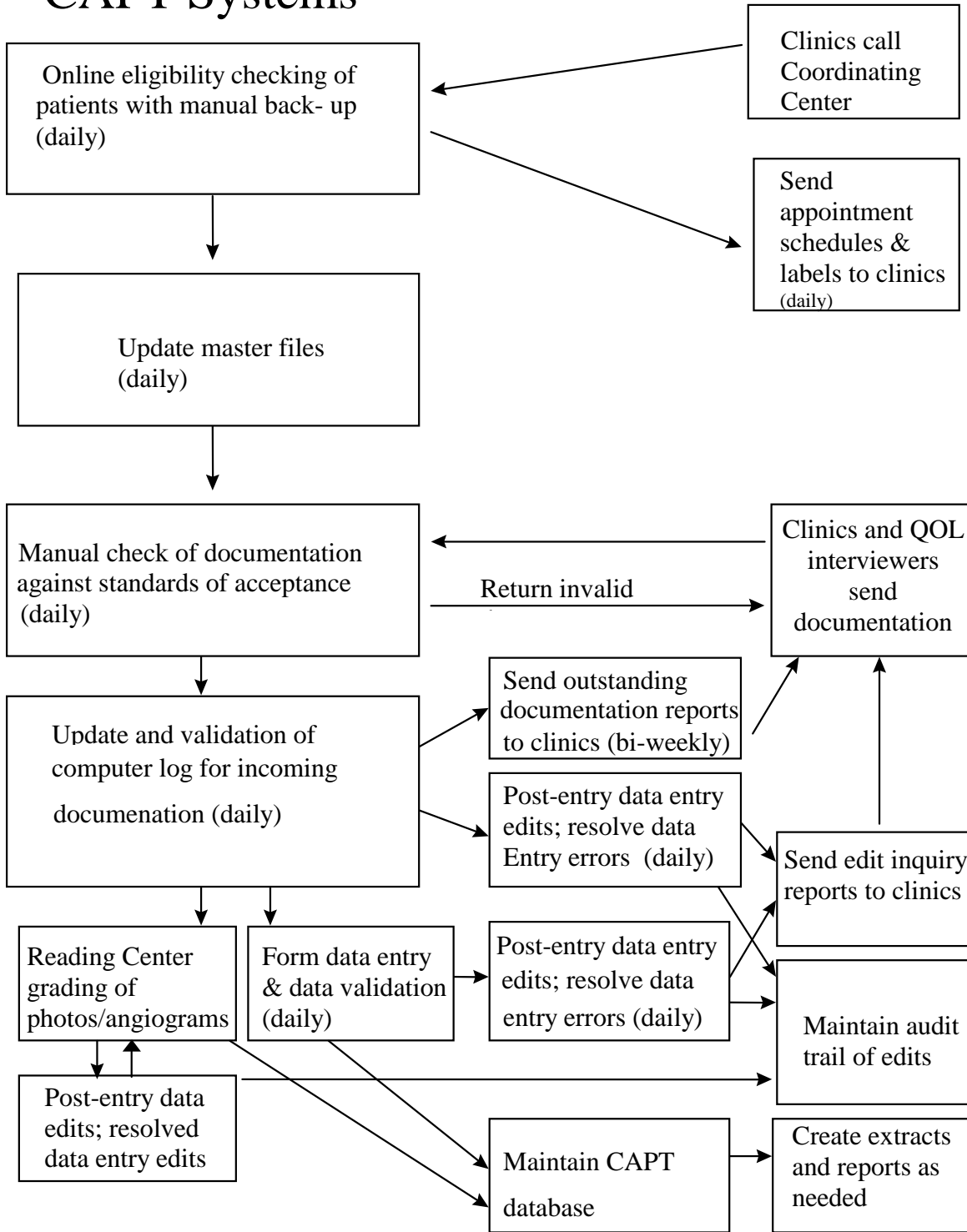
#### **18.10. COORDINATING CENTER HANDBOOK OF PROCEDURES**

The Coordinating Center investigators and staff are responsible for developing a Handbook of Procedures as a reference document for Coordinating Center staff and for others interested in Coordinating Center operations. The descriptions of procedures included in the Handbook are much more detailed than those included in this chapter and give step by step instructions for data processing tasks as well as many of the other activities of the Coordinating Center.

#### **18.11. MEETINGS OF THE COORDINATING CENTER**

Meetings of **all** members of the Coordinating Center will occur twice a month. Such meetings allow all members to remain up-to-date on study progress and discuss all aspects of a problem and ways to resolve the problem.

# CAPT Systems



## CHAPTER 19

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