

# **CATT**

**Comparison of  
Age-related Macular Degeneration  
Treatments  
Trials**

## **CATT: Lucentis<sup>®</sup> - Avastin<sup>®</sup> Trial**

### **Manual of Procedures**

#### **January 2011**

**COMPARISON OF AGE-RELATED MACULAR DEGENERATION  
TREATMENTS TRIALS (CATT)  
CATT: LUCENTIS® – AVASTIN® TRIAL**

**MANUAL OF PROCEDURES**

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# CHAPTER 1

## BACKGROUND

### 1.1. PUBLIC HEALTH IMPORTANCE

Age related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 in the United States and other Western countries (Tielsch, 1994; Sommer, 1991; Leibowitz, 1980; Klein, 1992; Sorsby, 1966; Buch, 2001). More than 1.6 million people in the US currently have one or both eyes affected by the advanced stage of AMD (Friedman, 2002) and it is estimated that there are another 7 million individuals “at risk” (The Eye Diseases Prevalence Research Group 2004). Once advanced AMD occurs in one eye, the risk for developing advanced AMD in the second eye over a 5 year period is 43% (AREDS, 2001) and the impact is substantial; more than 230,000 people in the United States are believed to be legally blind due to AMD (Tielsch, 1994). These numbers are expected to increase as the proportion of the American population over the age of 65 years increases. Projections by the US Census Bureau indicate the US population aged 65 years and older will increase 54% from 2000 to 2020 (US Census Bureau, 2002).

### 1.2. CLINICAL FEATURES OF AMD

The hallmark findings in an eye with AMD are the presence of drusen, atrophy of the retinal pigment epithelium (RPE), and pigmentary changes in the macula. These changes of early AMD are not usually associated with significant visual loss. However, progression to a more advanced stage may occur and is often associated with severe loss of vision. The advanced stage of AMD consists of either choroidal neovascularization (neovascular AMD) or central geographic atrophy. This progression to neovascular AMD or geographic atrophy is influenced by a variety of factors: smoking, advancing age, family history, white race, and low dietary intake of antioxidants (AREDS, 2005; Wang, 2003; Snow, 2000; Schaumberg, 2001; Pollack, 1998; Klein, 1998a, 1998b). However, the strongest risk factor is the size and extent (area) of the drusen and RPE changes themselves (AREDS, 2005).

The majority (90%) of the severe visual loss due to advanced AMD is attributable to the development of choroidal neovascularization (CNV) (Ferris, 1983; Sommer, 1991). These new vessels, which originate from the choroid, grow through breaks in Bruch's membrane and extend under the RPE and/or into the subretinal space. Approximately 70%-80% of neovascular lesions are subfoveal at the time of presentation (Berkow, 1984; Freund, 1993; Moisseiev, 1995; Margherio, 2000) and most of the lesions that develop outside the fovea, unless treated, expand into the fovea within one to two years. By three years after diagnosis, approximately 50% to 90% of eyes will have visual acuity of 20/200 or worse, depending in part on the fluorescein angiographic pattern of the lesion at presentation (MPS Group, 1991, 1993, 1994; Stevens, 1997; TAP, 2001; VIP, 2001). Neovascular lesions with a “classic” pattern of fluorescence generally deteriorate more rapidly and severely than eyes with an “occult” pattern of fluorescence (MPS Group, 1991).

### 1.3. PATHOGENESIS OF AMD

A variety of theories has been proposed regarding the pathogenesis of AMD which are well summarized in the literature (D'Amato, 1998; Husain, 2002; Ambati, 2003). There is good evidence that oxidative stress is involved in the development of AMD, a theory that received support from the beneficial effects of anti-oxidant vitamins that were observed in the Age-Related Eye Disease Study (Beatty, 2000; AREDS, 2001). Immune mediated processes have also been implicated in drusen formation and the inflammatory response associated by them may be an angiogenic stimulus (Penfold, 1985; Johnson, 2000; Hageman, 2001). The role that inflammation might play in the pathogenesis of AMD has been further elucidated by the finding by four independent laboratories that a variation in the factor H gene (HF1/CFH) dramatically increases the likelihood of developing AMD (Hageman, 2005; Haines, 2005; Edwards, 2005; Klein, 2005). Factor H is the major soluble inhibitor of the alternative pathway of complement activation and sustained complement activation can lead to chronic inflammation, aggravate local tissue damage, and contribute significantly to disease progression, such as that which occurs in Alzheimer's disease and atherosclerosis (Shen, 2003; Bok, 2005). It is not difficult to imagine how dysfunction of the complement system, which functions by creating holes in cell membranes as a first line of defense against microorganisms and other foreign particles (Bok, 2005), could produce RPE apoptosis as well as promote the development of microscopic breaks in Bruch's membrane which is preferentially thinner in the macula (Chong 2005).

The specific mechanism by which CNV develops is unclear. However, it is increasingly evident that a variety of cytokines that regulate angiogenesis play an important role. The delicate balance of polypeptide angiopromoters and angioinhibitors may be tipped in favor of neovascularization by the diffusion barrier that is created by diffuse thickening of Bruch's membrane from progressive accumulation of extracellular material containing lipid (drusen). This in turn interferes with normal functioning of the RPE (Ambati, 2003). RPE 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, choroidal blood flow has been shown to be impaired and choroidal perfusion altered in eyes with early AMD; these changes may also contribute to the accumulation of debris from the RPE and stimulation of angiogenesis (Pauleikhoff, 1990; Friedman, 1998). Examinations of surgical specimens excised from patients with CNV have provided immunohistopathologic evidence that growth factors such as vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF), transforming growth factor beta (TGF beta), angiopoietin 1, angiopoietin 2, and connective tissue growth factor (CTGF) are involved in the formation of CNV (Amin, 1994; Reddy, 1995; Kvanta, 1996; Otani, 1999; He, 2003). Of all of these cytokines, the one that has received the greatest attention to date is VEGF.

VEGF is a naturally occurring protein that is a potent inducer of angiogenesis. In addition, it is an even more potent inducer of vascular permeability (50,000 times greater than histamine) (Ferrara, 1992). There is also data that suggests that VEGF may also have pro-inflammatory properties (Ishida, 2003). The evidence that VEGF plays an important role in CNV is compelling. First, VEGF and VEGF receptors are expressed at high levels in areas of CNV in a primate model (Miller, 1994). Second, VEGF expression has been demonstrated in pathological examination of surgically excised CNV membranes of patients with AMD (Lopez, 1996). Third, VEGF has been shown to be present in CNV membranes of autopsied eyes with AMD (Frank, 1996). Finally, studies have shown that VEGF accumulates in vascular endothelial cells of

AMD patients (Asayama, 2000). These observations stimulated the development of several drugs that inhibit VEGF. The positive clinical trial results (discussed below) from the studies of these drugs validate the importance of VEGF in the pathogenesis of CNV and establish VEGF inhibition as an important treatment for neovascular AMD.

## **1.4. TREATMENTS FOR AMD**

Prior to 2005, there had been a number of advances in the treatment of neovascular AMD including the use of thermal laser, photodynamic therapy with verteporfin, and intravitreal injections of pegaptanib. While each of these treatments had been shown to be modestly effective at slowing the rate of visual loss, the overall experience with these treatments had been disappointing. The development of Lucentis®, a monoclonal antibody directed against VEGF, represents a major therapeutic improvement over existing therapies that has altered physicians' and patients' expectations regarding the extent of visual loss that can be prevented or reversed. The discussion that follows will first cover the treatments of AMD that preceded anti-VEGF therapy followed by discussion of the development of those drugs that inhibit VEGF.

### **1.4.1. Prevention**

In 2001, the Age-Related Eye Disease Study (AREDS) Group reported that daily supplementation with high-dose anti-oxidant vitamins (A, C, and E) and zinc reduced the 5-year incidence of a 3-line loss in vision from 29% to 23%, among patients with extensive drusen or with unilateral advanced AMD (AREDS, 2001). While this finding is of major importance, there is still much room for improvement in the prevention of vision loss from AMD. Specifically, 23% of patients still suffer loss of vision even if they are compliant with the AREDS supplements. Non-compliance with taking 2-4 tablets daily may be considerable among patients outside the environment of a clinical trial. Supplements cost \$200 per year and are not covered by health insurance.

Other preventative strategies being studied in randomized clinical trials include prophylactic laser treatment to eyes with extensive drusen (Complications of AMD Prevention Trial (CAPT Study Group, 2004; Prophylactic Treatment for AMD (Rodanant, 2002)) and posterior juxtасcleral injections of anecortave acetate (Retaane™) to the fellow eye in patients with unilateral advanced AMD. While there is hope that these strategies will be effective, neither is expected to eliminate the need for effective treatments for neovascular AMD.

### **1.4.2. Thermal Laser**

Between 1979 and 1994, the Macular Photocoagulation Study Group conducted clinical trials of thermal laser treatment for well-defined CNV (typically a classic pattern of leakage on fluorescein angiography). While treated eyes in all trials lost less visual acuity than untreated eyes, thermal laser treatment has serious limitations (MPS Group 1991, 1993, 1994). Not more than 20% of eyes that develop CNV are amenable to thermal laser treatment. Recurrent CNV develops in approximately half of treated eyes (MPS Group, 1986, 1990). In addition, thermal laser to subfoveal CNV causes an immediate drop in vision that many patients and ophthalmologists find unappealing despite the long term (18 to 24 months and beyond) benefit of treatment.

### 1.4.3. Photodynamic Therapy with Verteporfin

In 1999, the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group reported that photodynamic treatment (PDT) with verteporfin for eyes with subfoveal, predominantly classic CNV reduced the risk of loss of visual acuity (TAP Group, 1999). The proportion who lost fewer than 3 lines of visual acuity was 39% in the placebo group versus 67% in the treated group. Treatment benefit extends through at least 2 years (TAP Group, 2001). As a result, photodynamic therapy superseded thermal laser as the treatment of choice for subfoveal, classic CNV.

In 2001, the results of a clinical trial of PDT for eyes with subfoveal, occult CNV showed that treated eyes had better visual acuity at 2 years than untreated eyes (VIP Group, 2001). However, reduction in the risk of loss of fewer than 3 lines of visual acuity did not accrue until after 12 months and is modest (32% versus 45% at 24 months). In addition, PDT must be repeated up to every 3 months; the average number of treatments in the first 2 years is 5 to 6. Costs associated with treatment over 2 years are \$10,000 to \$15,000. These results and additional analyses led the Centers for Medicare and Medicaid Services (CMS) to cover PDT for predominantly classic CNV and occult and minimally classic lesions <4 disc areas in size (Blinder, 2003).

While the advent of PDT was a welcome addition to the treatment of neovascular AMD, the magnitude of the treatment effect was disappointing. At one year, the average patient in the TAP study lost vision despite treatment (mean of 10 letters). Only 6% of treated patients gained  $\geq 3$  lines and only 5% of patients retained vision of 20/40 or better (TAP Group, 1999). In an effort to improve visual outcomes, a number of investigators have begun to evaluate PDT in combination with an intravitreal injection of triamcinolone. Triamcinolone has the potential added benefit of reducing retinal edema and/or subretinal fluid and inhibits a number of cytokines that may contribute to CNV including VEGF. Consecutive case series have suggested that this combination treatment may be more effective than PDT alone (Spaide, 2005; Augustin, 2006). A randomized clinical trial designed to evaluate PDT and triamcinolone was suspended because the data from the Lucentis® trials and the availability of Avastin® resulted in no patients being enrolled.

### 1.4.4. Retaane®

Retaane® (anecortave acetate) is an angiostatic steroid that is not associated with intraocular pressure rise or acceleration of cataract (D'Amico, 2003). It has been shown to inhibit endothelial proliferation, endothelial migration and plasminogen activation. It is administered as a periocular posterior juxtасlеral depot injection every 6 months. In a phase II trial, visual acuity in patients (80%) with predominantly classic CNV treated with Retaane® 15 mg was better than in patients in the placebo group at one year by 3 measures: mean change from baseline vision ( $P = 0.01$ ), stabilization of vision (<3 line change, 79% Retaane® versus 53% placebo;  $P = 0.03$ ), and prevention of severe vision loss (decrease of  $\geq 6$  lines;  $P = 0.02$ ). A phase III trial involved 530 patients with predominantly classic CNV who were assigned to treatment with Retaane® or PDT. At one year, 45% of patients treated with Retaane® lost <3 lines of vision compared to 49% for patients treated with PDT ( $P = 0.43$ ). Although the point estimates of the two treatments were similar, Retaane® failed to meet its primary non-inferiority limit (Slakter, 2006). No clinically relevant drug or administration related safety issues have been identified in any clinical trial. At the time of this writing, Retaane® had been submitted to the FDA for consideration of approval. An additional clinical trial evaluating Retaane® for

prevention of CNV in 2500 patients at high risk for developing neovascular AMD is ongoing. Final results are not expected until 2010.

#### **1.4.5. Macugen®**

Macugen® (pegaptanib sodium) is an anti-VEGF aptamer that selectively binds to and neutralizes VEGF isoform 165 (Eyetechnology Study Group, 2002, 2003). In a phase III trial, 1186 patients with subfoveal CNV (all lesion types) were randomly assigned to treatment with one of three doses of Macugen versus sham injections (control) every 6 weeks for up to two years. At one year, the proportion of patients who had lost fewer than 15 letters (3 lines) was 70% for Macugen 0.3 mg versus 55% for the controls ( $p < 0.001$ ). No dose response relationship was observed. The therapeutic effect was not restricted to any lesion type. Like PDT, patients treated with Macugen continued on average to lose vision (7 letter mean loss at one year) and only 6% gained  $\geq 3$  lines. The most common serious adverse event was endophthalmitis which occurred in 1.3% of patients. Macugen received FDA approval in December, 2004.

#### **1.4.6. Lucentis®**

Lucentis® (ranibizumab, formerly RhuFab V2) is a modified fragment of an anti-VEGF antibody (Avastin®) that binds and inhibits all VEGF isoforms (Krzystolik, 2002). Initial studies with the full length antibody suggested that it did not penetrate the retina when injected into the vitreous cavity (Mordenti(a), 1999). However, the Fab fragment passed easily through the retina to reach the target (subretinal) space. An affinity maturation process was applied to increase the binding affinity to VEGF 140-fold, and Lucentis® was moved into clinical studies. The results from four large randomized clinical trials have been reported to date.

In a phase III trial (entitled MARINA), 716 patients with occult and minimally classic CNV were randomly assigned to one of two doses of Lucentis® (0.3 mg or 0.5 mg) versus sham injections every 4 weeks (fixed schedule) for up to two years. At one year, the proportion of patients who had lost  $< 15$  letters (3 lines) was 95% for both 0.3 mg and 0.5 mg of Lucentis® versus 62% for the controls ( $p < 0.001$ ). Unlike all previous AMD studies, the average patient gained vision with a mean improvement from baseline of 7 letters (compared to a 10 letter loss among controls). The proportion of treated patients who gained  $\geq 3$  lines was 25% for Lucentis® 0.3 mg and 34% for the 0.5 mg dose. The proportion of patients who retained vision of 20/40 or better was 39% and 40% respectively (Rosenfeld, 2006). The 2-year results showed that the large treatment benefit was maintained with injections given every 28 days. The mean difference between controls and the Lucentis® treatment groups was 20.3 letters for the 0.3mg dose and 21.3 for the 0.5mg group.

In a second study (entitled FOCUS), 162 patients with predominantly classic subfoveal CNV were randomly assigned to PDT versus Lucentis® 0.5 mg + PDT. At one year, the proportion of patients who had lost  $< 15$  letters (3 lines) was 91% in the combined Lucentis® + PDT group versus 68% for the PDT alone group ( $p < 0.003$ ). Patients treated with PDT + Lucentis® gained vision on average while those treated with PDT alone lost vision (mean change of +5 letters versus -8 letters) The proportion of patients who gained  $\geq 3$  lines was 24% for Lucentis® + PDT versus 5% for PDT alone. The mean number of PDT treatments was 3.4 in the PDT alone group versus 1.3 in the combined group (unpublished data, presented at the ASRS Meeting, July, 2005). Two year results, with data complete on approximately 85% of patients, were similar on all outcome measures; e.g., the difference in mean change in visual acuity was 12.4 letters at two

years whereas the difference at 1 year was 13.1 letters (unpublished data, presented at the ASRS Meeting, September, 2006).

In a third study (entitled ANCHOR), 423 patients with predominantly classic subfoveal CNV were randomly assigned 2:1 to Lucentis® (0.3 mg or 0.5 mg) given every 4 weeks (fixed schedule) versus PDT every 3 months as needed for up to two years. At one year, the proportion of patients who had lost <15 letters (3 lines) was 94% in the 0.3 mg group, 96% percent in the Lucentis® 0.5 mg group versus 64% percent for the PDT group ( $p < 0.0001$ ). Patients treated with Lucentis® gained vision on average while those treated with PDT lost vision. (Brown, 2006)

In a fourth study (entitled PIER), 184 patients with predominantly classic, minimally classic or occult with no classic lesions received a 0.3-mg or 0.5-mg intravitreal injection of Lucentis® or sham injection once a month for the first three months followed by injections once every three months. At month three, on average, patients treated with Lucentis® gained 2.9 letters (0.3mg) or 4.3 letters (0.5mg) and patients in the sham injection group lost 8.7 letters. At month 12, on average, patients treated with Lucentis® lost 1.6 letters (0.3mg) or 0.2 letters (0.5mg) and patients in the sham group lost 16.3 letters ( $p < 0.0001$ ). The proportion of patients in the fixed, quarterly schedule Lucentis® groups losing < 15 letters at 12 months was 83% (0.3mg) or 90% (0.5mg) compared to 49% for patients receiving sham injections. (Genentech press release, June 2, 2006).

Adverse events reported to date been minimal. Conjunctival hemorrhage, eye pain, and increased intraocular pressure are common, mild to moderate side effects. The incidence of endophthalmitis was 0.4% – 0.8% in the MARINA study. Intraocular inflammation was noted in 8.6% of patients in the FOCUS study. However, the FOCUS trial employed a lypholyzed formulation that was discontinued before MARINA and ANCHOR began. The rate of inflammation was 0.8% in MARINA using the newer formulation. There were no reported cases of endophthalmitis in the PIER study.

There is an ongoing study evaluating a less frequent dosing schedule. PRONTO is a single center, uncontrolled, case series of 40 patients treated with Lucentis. After an initial 3 (0.5 mg) injections, additional injections are given only if specific clinical criteria are met: a loss of 5 letters in conjunction with fluid in the macula as detected by OCT, an increase in OCT central retinal thickness of at least 100  $\mu\text{m}$ , new onset classic CNV, new macular hemorrhage, or persistent macular fluid detected by OCT at least 1 month after the previous injection. The mean number of treatments within the first year was 5.5. The proportion of eyes with an increase in visual acuity of 3 or more lines was 35% and the mean gain was 9.3 letters.

Lucentis® received approval (US BL 125156) for treatment of neovascular AMD on June 30, 2006.

#### **1.4.7. Avastin®**

##### **1.4.7.1. Rationale for use of Avastin®**

Bevacizumab (Avastin®) and Lucentis® are derived from the same monoclonal antibody. Avastin® was FDA-approved in 2003 for intravenous use in patients with colorectal cancer (Hurwitz, 2004). In a series of 18 patients with CNV, intravenous administration of Avastin®

was associated with improved visual acuity and reduced retinal thickness (Michels, 2005). Systemic administration of Avastin® is associated with an increased risk of thromboembolic events in cancer patients (Herbert, 2005).

Following the encouraging clinical trial results with Lucentis®, several investigators began evaluating intravitreal Avastin® for the treatment of CNV. Given its molecular similarity to Lucentis, its low cost, and its availability, the interest in Avastin® has been considerable. Within 6 months of its public introduction as a single case report at the ASRS meeting in July 2005 (Rosenfeld, 2005) it has been adopted as a first line therapy for CNV by many retina specialists in the United States, despite the absence of any randomized clinical trial data to support its intraocular use. In our discussions with a number of prospective collaborators for this study, it became apparent that the number of patients treated with intravitreal Avastin® in the last 3 months alone far exceeds the number of patients in all of the Lucentis® trials combined. The reasons for this are its apparent beneficial effect and its availability for off-label use. Although preclinical primate data suggested that a 149 kD antibody the size of Avastin® injected into the vitreous cavity would not penetrate the retina, in clinical practice, intravitreal Avastin® has been found to have a significant biological effect on retinal edema, subretinal fluid, and pigment epithelial detachments secondary to AMD with concomitant improvement in visual acuity (Avery, 2006; Rich, 2006; Yoganathan, 2006). In addition, when Avastin® was injected into the vitreous of rabbits, it showed full penetration of the retina (Shahar, 2006; Feiner, 2006; Schraemeyer, ARVO 2006).

#### **1.4.7.2. Dose of Avastin®**

The Avastin® dose most commonly used in the United States is 1.25 mg in 0.05 ml. This dose was derived from consideration of the molecular weight and binding affinity differences between Lucentis® and Avastin, as well as the differences in presumed retinal penetration. It is estimated that Avastin® 1.25 mg may be roughly equivalent to Lucentis® 0.3 to 0.5 mg in terms of the number and affinity of the binding sites that are delivered to the eye (Rosenfeld, 2005). However, outside of the United States, 2.50 mg in 0.10 ml is used frequently. (Bashshur, 2006). A dose-escalation study of a single injection of Avastin® to 15 patients in each of 3 dose groups (1.0mg, 1.5 mg, and 2.0 mg) showed nearly identical improvements in LogMAR visual acuity for the 1.5 mg and 2.0 mg doses at 1 and 6 weeks after injection (Costa, 2006). However, at 12 weeks, the mean improvement decreased from the 6-week level in the 1.5 mg group but was stable in the 2.0 mg group. Improvements in visual acuity in the 1.0 mg group were less than in the higher dose groups and also decreased between 6 and 12 weeks. The dose-response effect for change in visual acuity from baseline across the 3 groups at 12 weeks was statistically significant at the  $p=0.02$  level. These data provide some evidence that the longevity of the treatment effect is dose-dependent in the 1.0 to 2.0 mg range.

#### **1.4.7.3. Duration of activity**

The intravitreal half-life of Avastin® is estimated to be twice that of Lucentis® (Mordenti(b), 1999). This is thought to be due to the increased size of Avastin® (149 kD versus 48 kD for Lucentis®) as well as the presence of the Fc portion. A longer half-life may allow a therapeutic effect to be achieved with less frequent injections. However, the optimal dosing schedule is unknown. As a result, retreatment with Avastin® has been primarily “as needed,” that is, driven by the clinical response.

#### 1.4.7.4. Safety of Avastin® as reported in the grant application for the clinical trial

To date, the safety profile of Avastin® has been very good. The solution is non-preserved and is not known to contain any additives that would be toxic to the retina (Rosenfeld, 2005). Avastin® is non-toxic, as measured by electroretinogram, to the retina of the rabbit, mouse, and cow (Shahar, 2006; Feiner, 2006; Manzano, 2006; Heiduschka, ARVO 2006; Luke, ARVO 2006) Electroretinography after injection of Avastin® in human eyes has also not shown any deleterious effect (Maturi, 2006). No negative effects were observed on retinal pigment epithelial, neurosensory retinal, or microvascular endothelial cells in vitro when treated with doses similar to or above the doses in clinical use (Luthra, 2006).

There has been widespread use throughout the world of Avastin® for neovascular AMD as well as for diabetic macular edema and other retinal-vascular diseases. Large, systematic studies of the safety of Avastin® are lacking; however, a review of 47 abstracts for the ARVO 2006 meeting provided data on 4,845 patients receiving one or more intravitreal injections of Avastin. In 30 of the studies, no adverse events were reported. In addition to the more severe adverse events listed below, corneal abrasions (8), inflammation (6), foreign body sensation and subconjunctival hemorrhage (5), ocular pain (2), punctate keratitis (1), and elevated IOP (1) were reported.

##### **Non-Ocular Adverse Events**

- 2 Deaths\*
- 2 Cerebrovascular accidents
- 1 Transient ischemic attack
- 1 Ischemic colitis 2 wks post injection
- 1 Bowel stricture (history of bowel surgery)
- 10 elevated blood pressure

##### **Ocular Adverse Events**

- 1 Endophthalmitis
- 1 Retinal detachment
- 1 CRAO
- 1 Vitreous hemorrhage
- 4 Acute vision loss
- 1 lost 4 lines of VA
- 3 new/increased subretinal hemorrhage

\* 1 cerebral hemorrhage 2 weeks after injection in a patient with pre-existing hypertension, diabetes, and anti-coagulation, 1 cause unknown.

While the types of reporting cited above may underestimate the true incidence of adverse events, the widespread use and very low reported incidence of serious side effects provide sufficient evidence of safety to move forward with a well-controlled clinical trial involving Avastin.



#### 1.4.8. Summary of Treatment Efficacy for Neovascular AMD at One Year

	< 3 Line Loss	≥ 3 lines gained	≥ 20/40
<u>Natural History</u>			
Pred Classic	39%	2%	1%
Occult	51%	2%	7%
<u>Thermal Laser</u>			
	50%	1%	----
<u>Photodynamic Therapy</u>			
Pred Classic	67%	6%	5%
Occult	55%	3%	15%
<u>Anti-VEGF agents</u>			
<u>Macugen</u>			
	70%	6%	----
<u>Lucentis*</u>			
Pred Classic	95%	38%	35%
Min Classic/Occult	95%	34%	40%

\*Percentages average over the 0.3mg and 0.5mg groups which had nearly identical results.

#### 1.5. RATIONALE FOR TREATMENT COMPARISONS

Lucentis® is the most effective treatment for neovascular AMD studied to date and has become the standard of care. However, widespread implementation of a fixed, every 4 week dosing schedule has obvious practical limitations and the cost of such repeated injections is considerable. Avastin® has not been evaluated relative to Lucentis®. Although the half-life of Avastin® may be longer than the half-life of Lucentis, dosing as frequently as every 28 days with Avastin® may still be necessary to achieve the same beneficial effects as Lucentis®. Previous studies do not answer the question of whether a reduced dosing schedule is as effective as a fixed schedule of monthly injections. The PIER study showed that a schedule of dosing every three month was more effective than a sham injection, but did not allow comparison with either a fixed schedule or a schedule dependent upon clinical response. The PRONTO study showed that a dosing schedule for Lucentis® dependent on clinical response could be carried out and achieve favorable responses, however, there was no comparison with fixed schedule treatment. Treatment dependent on clinical response has the potential to reduce the treatment burden to patients as well as to reduce the overall cost of therapy.

In September 2006, the National Eye Institute (NEI) awarded funding for the Comparison of AMD Treatments Trials: Lucentis-Avastin Trial. NEI funds support research activities in the clinical centers, Coordinating Center, Reading Centers, and Study Chair's Office. The multicenter, randomized, clinical trial will involve 4 treatment groups:

- 1) Lucentis® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Lucentis® every 4 weeks or to variable dosing.
- 2) Avastin® on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Avastin® every 4 weeks or to variable dosing.

- 3) Lucentis® on a variable dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.
- 4) Avastin® on a variable dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.

## CHAPTER 2

### OVERVIEW OF THE CATT: LUCENTIS-AVASTIN TRIAL DESIGN

#### 2.1. COMPARISON OF AMD TREATMENT TRIALS (CATT)

CATT is envisioned as a set of multicenter, randomized clinical trials of treatments for neovascular age-related macular degeneration (AMD). The trials will differ predominantly in the treatments under evaluation. The trials will share the same overall methods and structure; e.g., common standardized procedures for measurement of outcome measures, data collection and management methods, and similar committee and administrative structure. The Lucentis-Avastin Trial will be the first CATT clinical trial.

#### 2.2. CATT: LUCENTIS-AVASTIN TRIAL

The CATT: Lucentis-Avastin Trial will identify the best approach to anti-VEGF therapy to be used as the standard of comparison for subsequent clinical trials for neovascular age-related macular degeneration. A summary of the trial design elements are displayed in Table 2-1. While the remainder of this manual of procedures addresses details of many of the topics, some comments about the choice of specific approaches are provided below:

- **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. There are no criteria regarding the angiographic pattern of leakage (classic, occult choroidal neovascularization {CNV}) or the size of the lesion. Lucentis<sup>®</sup> has shown efficacy in preserving visual acuity in clinical trials involving eyes with both types of leakage. Patients with visual acuity in the eligible range (20/25 to 20/320) may benefit from stabilization or improvement of vision, regardless of the initial size of the lesion. The vast majority of patients with new, subfoveal CNV are eligible for the CATT: Lucentis-Avastin Trial.
- **Treatment in the CATT: Lucentis-Avastin Trial will be in two phases**, the first year and the second year. The primary outcome assessment is at 12 months; however, it will be important to know the need for and outcome of treatment beyond one year. In addition, the results of the Study will not be known when patients complete 12 months of follow-up, so there will be no evidence-based guidelines for treatment beyond 12 months. Patients in the two variable dosing arms will continue with their initially assigned treatments. However, even if Lucentis<sup>®</sup> or Avastin<sup>®</sup> on fixed schedule provides better visual acuity at one year than the other treatment arms, there will still be the question of whether treatment every four weeks must continue indefinitely. A randomly selected half of the patients assigned initially to fixed schedule treatment will be assigned to variable treatment (with the originally assigned study drug) for the second year. Re-randomization allows for estimation of the change in visual acuity during the second year under the two treatment strategies and allows for relatively precise estimation of (95% confidence interval of  $\pm 3$  letters) of the difference between the two groups. This information will be very valuable if the two variable dosing arms prove inferior to fixed schedule Lucentis<sup>®</sup> at 1 year.

**Table 2-1. CATT: Lucentis-Avastin Trial Design Summary**

<b>Feature</b>	<b>Criteria</b>
Objective	Evaluate the relative efficacy and safety of treatment of subfoveal neovascular AMD with Lucentis <sup>®</sup> on a fixed schedule, Avastin <sup>®</sup> on a fixed schedule, Lucentis <sup>®</sup> on a variable schedule, and Avastin <sup>®</sup> on a variable schedule
Major Eligibility Criteria	Active subfoveal choroidal neovascularization (CNV) Fibrosis < 50% of total lesion area Visual acuity (VA) 20/25-20/320 Age ≥ 50 yrs ≥1 drusen (>63μ) in either eye or late AMD in fellow eye No previous treatment for CNV in study eye No other progressive retinal disease likely to compromise VA No contraindications to injections with Lucentis <sup>®</sup> or Avastin <sup>®</sup>
Randomization Unit	Person, only one eye of each person may be enrolled
Masking	VA examiner; image graders masked to drug and schedule; Ophthalmologist masked to drug
Treatments	1) <u>Lucentis<sup>®</sup></u> on a <u>fixed</u> schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Lucentis <sup>®</sup> every 4 weeks or to variable dosing. 2) <u>Avastin<sup>®</sup></u> on a <u>fixed</u> schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Avastin <sup>®</sup> every 4 weeks or to variable dosing. 3) <u>Lucentis<sup>®</sup></u> on a <u>variable</u> dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity. 4) <u>Avastin<sup>®</sup></u> on a <u>variable</u> dosing schedule for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity.
Outcome Measures	1° Mean change in VA at 1 year (non-inferiority limit of 5 letters)
(at 1 year and 2 years)	2° Number of treatments 3-line change in VA (15 letters on ETDRS chart) Change in subretinal and intraretinal fluid on optical coherent tomography Change in lesion size on fluorescein angiography Incidence of endophthalmitis, retinal detachment, cataract, uveitis Incidence of adverse events Cost
Sample size	300 per group, or 1200 total
Follow-up	Every 4 weeks through 2 years

- **The guiding principle for variable dosing schedule Lucentis® or Avastin®** is that Lucentis® and Avastin®, as anti-VEGF agents, have anti-permeability and anti-angiogenesis properties and that treatment should be given only when there are signs of neovascular AMD that are associated with abnormal vessel permeability or vessel growth.
- The fact that patients in the fixed schedule Lucentis® and Avastin® arms receive injections every month regardless of response to treatment, while those in the two variable dosing arms do not, unmask the patient, the ophthalmologist, and Clinic Coordinator to whether the patient is in a fixed schedule group or a variable dosing arm. However, ophthalmologists and visual function examiners are masked to whether patients are receiving Lucentis® or Avastin®. **Thus, interpretations of OCTs and angiograms by the ophthalmologist with respect to meeting requirements for retreatment are masked.** Including sham injections for patients who do not meet the criteria for retreatment was considered by the Planning Committee but rejected for the following reasons: 1) patients receiving both types of injection may be able to distinguish between a real injection and a sham injection; 2) the logistical aspects of allowing for the possibility of a sham injection or real injection at each visit increases the likelihood of mistakes in treatment and increases the overall complexity of the trial.
- Given the underlying continuous measurement scale of visual acuity, the high likelihood for both increases and decreases in visual acuity score, and the inability of the traditional 3-line loss dichotomy to accommodate measurement of further improvements in treatment efficacy, **mean change is a strong choice for the primary outcome.** The higher precision in estimation of a mean relative to a proportion is desirable in non-inferiority trials where the interpretation is driven by the width of the confidence interval. The only major drawback to the choice of using mean change is the absence of a description of differences between groups in clinically meaningful changes in the distribution. However, this shortcoming can be overcome by secondary outcome measures and through the use of descriptive statistics.
- Despite the strong reliance in the Trial on OCT for determining the need for treatment, there is a need for assessing whether OCT, FA, and visual acuity associations present at the time of diagnosis of CNV persist over the course of treatment and whether the short-term responses to treatment in these features provide prognostic information independent of the prognostic information at baseline. **The OCT and Fluorescein Angiography Substudy addresses this need.**
- CATT procedures for refraction, visual acuity measurement, and photography are the same as those used in other multicenter clinical trials for retinal diseases.

## CHAPTER 3

### PATIENT SELECTION

#### 3.1. PATIENT SELECTION

Patients will be randomized in a 1:1:1:1 ratio among 1) Lucentis<sup>®</sup> treatment on a fixed schedule of every 4 weeks, 2) Avastin<sup>®</sup> treatment on a fixed schedule of every 4 weeks 3) Lucentis<sup>®</sup> on a variable dosing schedule and 3) Avastin<sup>®</sup> on a variable dosing schedule. Patient inclusion and exclusion criteria in the CATT: Lucentis-Avastin Trial are based in large part on the criteria specified in the protocols for the previous clinical trials of Lucentis<sup>®</sup>. Lucentis-Avastin Trial patients will have only one eye enrolled in the study.

Written informed consent will be obtained before initiation of any study-specific procedures. Screening evaluations may be performed at any time within the 7 days preceding the day of randomization when the first study injection is expected to be given.

##### 3.1.1. Inclusion Criteria

All patients must meet the following criteria for entry into the CATT: Lucentis-Avastin Trial:

- Signed informed consent form
- Age  $\geq$  50 years of either gender
- Women must be postmenopausal for at least 12 months prior to trial entry, or surgically sterile. If of child bearing potential, a serum pregnancy test with a negative result must be obtained within 14 days prior to the first treatment. Women of child bearing potential must be practicing effective contraception implemented during the trial and for at least 60 days following the last dose of study medication.
- No condition that precludes follow-up for 2 years.
- No contraindication to intravitreal injection of Lucentis<sup>®</sup> or Avastin<sup>®</sup>, as specified in the exclusion criteria below.

##### 3.1.2. Eligibility criteria for study eyes

**Study eyes** must meet the following criteria for entry into the CATT: Lucentis-Avastin Trial:

- Newly diagnosed, angiographically documented, previously untreated, active CNV lesion (i.e., leakage on fluorescein angiography AND subretinal, intraretinal, or sub-RPE fluid on OCT) secondary to age-related macular degeneration.
- Best corrected visual acuity in the study eye, using e-ETDRS testing, between 20/25 and 20/320 (Snellen equivalent), inclusive.

Only one eye will be enrolled in the Study. If both eyes are eligible, the patient and study ophthalmologist will select the eye for entry.

- The CNV or sequela of the CNV (i.e., pigment epithelium detachment, subretinal or sub-RPE hemorrhage, blocked fluorescence, macular edema, or subretinal sub-RPE or intraretinal fluid) must involve the center of the fovea.
- The total area of fibrosis must comprise less than 50% of the total lesion.
- $\geq 1$  drusen ( $>63$  microns) in either eye OR late AMD in fellow eye
- No previous treatment for CNV in the study eye
- Clear ocular media and adequate pupillary dilation to permit good quality fundus imaging.
- Disc and macula color stereoscopic photographs and fluorescein angiogram within 7 days of randomization.
- OCT of the macula within 7 days of randomization.

### **3.2. EXCLUSION CRITERIA**

Subjects who meet any of the following criteria will be excluded from study entry:

#### **3.2.1. Prior/Concomitant Treatment**

- Previous treatment with verteporfin PDT, Macugen<sup>®</sup>, Lucentis<sup>®</sup>, intravitreal Avastin<sup>®</sup>, thermal laser, external beam radiation or other AMD therapy in the study eye. Prophylactic treatment such as CAPT/CNVPT treatment does not exclude the patient.
- Previous treatment with intravenous Avastin<sup>®</sup>
- Concurrent treatment with an investigational drug or device in the non-study eye for any ocular condition
- History of submacular surgery or other surgical intervention for AMD in the study eye
- Previous participation in any studies of investigational drugs likely to have ocular effects within 30 days preceding the initial study treatment
- Concurrent use of systemic anti-VEGF agents.

#### **3.2.2. Exclusionary Lesion Characteristics**

- Fibrosis or geographic atrophy involving the center of the fovea in the study eye
- CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia
- Retinal pigment epithelial tear involving the macula in the study eye

### **3.2.3. Exclusionary Concurrent Ocular Conditions**

- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye
- Current vitreous hemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole in the study eye
- History of vitrectomy in the study eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
- For subjects who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 8 diopters of myopia.
- Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding the first study treatment.
- Uncontrolled glaucoma in the study eye (defined as intraocular pressure  $\geq 25$  mmHg despite treatment with antiglaucoma medication)
- Patients who are unable to be photographed to document CNV due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV.
- Patients with other progressive retinal disease likely to affect visual acuity within the next 2 years. Patients with pattern dystrophy with CNV and drusen determined to be definitely AMD are eligible.
- Patients with other ocular diseases that can compromise the visual acuity of the study eye such as amblyopia and anterior ischemic optic neuropathy

### **3.2.4. Concurrent Systemic Conditions**

- Premenopausal women not using adequate contraception (see Section 3.3)
- Pregnancy or lactation
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications
- Current treatment for active systemic infection



- Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders
- History of recurrent significant infections or bacterial infections
- Inability to comply with study or follow-up procedures

### 3.3. DEFINITION OF TERMS PERTAINING TO ELIGIBILITY CRITERIA

**Informed Consent:** Written informed consent must be obtained from each patient prior to performing any study-specific procedures. The patient should be asked to sign the consent form only after the patient has been introduced to the study and had questions answered.

**Age:** Few patients below the age of 50 are anticipated to meet the criteria below. Patients below the age of 50 may have forms of macular degeneration other than age-related macular degeneration.

**Images:** Stereoscopic color photographs of the disc and macula of both eyes are required. In addition, a fluorescein angiogram with the early phase on the study eye is mandatory. An OCT of each eye is also required. All images must be taken within 7 days prior to randomization.

**Effective Contraception:** Acceptable methods of birth control are surgical sterilization, use of oral contraceptives, barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel, an intrauterine device (IUD), or contraceptive hormone implant or patch.

**Condition Precluding Follow-Up:** Patients must have a high probability of completing 2 years of follow-up. The mere presence of serious health conditions 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 CATT clinical center should not be enrolled.

**Contraindications to Lucentis<sup>®</sup> or Avastin<sup>®</sup> injections:** No previous inflammatory reactions following intravitreal Lucentis<sup>®</sup> or Avastin<sup>®</sup> treatment in the non-study eye.

**Active CNV** includes **both** of the following: leakage on fluorescein angiography AND subretinal or intraretinal fluid on OCT.

**CNV lesion:** A contiguous area of abnormal tissue in the macula that encompasses angiographically documented CNV with possible additional components of subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the retinal pigment epithelium, and fibrosis.

**AMD:** Clinical and/or angiographic signs consistent with AMD (e.g., drusen, retinal pigment epithelial changes, choroidal neovascularization) with no other likely etiologic explanations for the degenerative changes.

**Sequela of CNV:** Sequela of the lesion includes pigment epithelial detachment, subretinal, sub-RPE hemorrhage, blocked fluorescence, macular edema, or subretinal, sub-RPE or intraretinal fluid contiguous with the CNV lesion.

**Visual Acuity Score:** The best corrected E-ETDRS visual acuity score for a study eye must be  $\geq 23$  letters (20/320 or better) and  $\leq 82$  letters (20/25 or worse).

**Cataract Surgery:** Eyes that have had lens extraction or lens implantation within the last 2 months are ineligible. Eyes that have had a capsulotomy within the past 2 months are ineligible.

**Lens Opacities:** Lens opacities may be present but must be such that at enrollment and for the next 2 years the view of the posterior pole for ophthalmoscopy and photography is unobstructed. Patients likely to undergo cataract extraction in the study eye within the next 2 years should not be enrolled in the Lucentis-Avastin Trial Study.

**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 2 years excludes the patient from the study.

### **3.4. PATIENT RECRUITMENT AND SCREENING**

#### **3.4.1. Patient Recruitment**

Lucentis-Avastin Trial patients will be recruited through a variety of methods. Most patients will be identified from the clinical practices at the participating centers and from referring ophthalmologists in the community. To aid recruitment efforts, the CATT Coordinating Center will develop materials both for referring ophthalmologists and for patients explaining the study. All centers must submit these materials to their local IRB for approval prior to their distribution to potential patients.

#### **3.4.2. Patient Screening**

The Study enrolling ophthalmologist must determine a patient's eligibility prior to enrollment. All patients must undergo an ophthalmological examination, fluorescein angiography, color photography and OCT to assess whether the patient meets ocular eligibility criteria, visual function testing conducted according to Lucentis-Avastin Trial study protocol to determine if visual acuity requirements are met, and respond to questions concerning medical history that may impact their eligibility for the Lucentis-Avastin Trial. All procedures to determine eligibility must be completed within 7 days prior to randomization with the exception (14 days) of pregnancy testing for women of childbearing potential. (For details on these procedures, refer to section 5.2 of this protocol).

#### **3.4.3. Participation in Other Clinical Trials**

##### **3.4.3.1. AREDS2 Participation**

Patients who are participating in the Age-Related Eye Diseases Study 2 (AREDS2) may participate in the CATT: Lucentis-Avastin Trial if they meet all other Study eligibility criteria.

Pre-enrollment approval from the Coordinating Center is not required; however, the clinic coordinator must note AREDS2 participation on the Baseline General Information Form.

#### **3.4.3.2. Participation in Other Studies**

If a prospective patient is participating in another study other than AREDS2, either ocular or non-ocular, the enrolling ophthalmologist or clinic coordinator must contact the Director of the Coordinating Center prior to enrolling the patient into CATT. The ophthalmologist and clinic coordinator should obtain as much information as possible about the other study so that an appropriate decision, that safeguards both the patient's safety and the objectives of the study, can be made.

## CHAPTER 4

### STUDY DRUG AND TREATMENT

#### 4.1. INTRODUCTION

The treatment protocols used in the CATT: Lucentis-Avastin Trial have evolved from the methods used by other investigators in earlier studies of intravitreal anti-VEGF agents for subfoveal choroidal neovascularization. Injection procedures have been adapted from the DRCRnet standard procedures.

Patients will be randomized in a 1:1:1:1 ratio to one of the four treatment groups listed below. Criteria for additional treatment in the two variable dosing schedule arms are defined in section 4.4.2:

- a. Lucentis<sup>®</sup> on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Lucentis<sup>®</sup> every 4 weeks or to variable dosing
- b. Avastin<sup>®</sup> on a fixed schedule of every 4 weeks for 1 year; at 1 year, re-randomization to Avastin<sup>®</sup> every 4 weeks or to variable dosing
- c. Lucentis<sup>®</sup> on variable schedule dosing for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity
- d. Avastin<sup>®</sup> on variable schedule dosing for 2 years; i.e., after initial treatment, monthly evaluation for treatment based on signs of lesion activity

Patients will follow their assigned protocols for two years after their enrollment.

#### 4.2. TREATMENT OF PATIENTS INITIALLY ASSIGNED TO FIXED SCHEDULE LUCENTIS<sup>®</sup> OR AVASTIN<sup>®</sup>

All patients who are assigned to receive study drugs on a fixed schedule will receive an intravitreal injection of either Lucentis<sup>®</sup> or Avastin<sup>®</sup>, as appropriate, immediately after receipt of the randomized treatment assignment and every 4 weeks through 48 weeks of follow-up. The intent of the study protocol for patients assigned to fixed schedule treatment is treatment every 4 weeks (e.g., 28 days) but the *minimal* interval between treatments may be 23 days. The protocol will continue to use the term “monthly” treatments to reflect the study’s objective of 28 day treatment intervals. Patients should receive 12 additional injections during the first 48-week follow-up period, unless contraindications develop. The dose per injection will be:

- 0.5 mg (0.05 mL) of Lucentis<sup>®</sup>
- 1.25 mg (0.05 mL) of Avastin<sup>®</sup>

At week 52 there is a second randomization for patients originally assigned to one of the fixed schedule treatment groups. Half of the patients in each fixed schedule group will continue on the fixed schedule (injection every month), while the other half will be assigned to a variable schedule for the next year.

- Patients assigned to remain on fixed schedule injections will receive injections at week 52 and every 4 weeks through 100 weeks. Patients should receive 13 additional injections during this period, unless contraindications develop.
- Patients assigned to variable schedule injections will be assessed for treatment at week 52 and every 4 weeks through 100 weeks. The decision to treat patients will follow the treatment guidelines described below in section 4.3.

At 104 weeks, the last follow-up visit for the clinical trial will occur. No treatment will be performed during the visit at 104 weeks as part of the clinical trial treatment protocol.

#### **4.2.1. Policy on Treatment Futility for Patients Assigned to Fixed Monthly Treatments**

Patients assigned to a fixed schedule of Lucentis or Avastin should receive monthly injections throughout the period of treatment assignment, either 1 or 2 years. However, during the course of treatment, some patients will develop severe permanent loss of vision due to progression of their disease. If in the best medical judgment of the treating ophthalmologist it is believed that there is no chance of any benefit to the patient from additional intravitreal injections in terms of preserving vision or retinal anatomy, intravitreal injections of the study drug may be suspended. Examples of this scenario would include patients with very large areas of central atrophy or subretinal fibrosis who have no evidence of residual macular function.

These patients will continue to be followed in the study at regular monthly intervals. It would be exceedingly uncommon to reach a point of treatment futility during the first 12 months of follow-up

### **4.3. LUCENTIS<sup>®</sup> AND AVASTIN<sup>®</sup> TREATMENT ON VARIABLE SCHEDULE DOSING FOR THE FIRST 104 WEEKS**

#### **4.3.1. Initial Treatment**

All patients who are randomized to receive study treatment on variable scheduled dosing will receive an intravitreal injection of either Lucentis<sup>®</sup> or Avastin<sup>®</sup>, as appropriate, immediately after receipt of the randomized treatment assignment. This is the only mandatory treatment for these patients. The dose per injection will be:

- 0.5 mg (0.05 mL) of Lucentis<sup>®</sup>
- 1.25 mg (0.05 mL) of Avastin<sup>®</sup>

An ophthalmologist, who remains masked to the identity of the study drug (Lucentis<sup>®</sup> or Avastin<sup>®</sup>), performs the ophthalmologic examination during follow-up, and evaluates OCTs and fluorescein angiograms (when performed) to determine if the eye should be treated. The ophthalmologist administers the injection to the patient whenever he/she judges that treatment is warranted based on the guidelines below.

#### **4.3.2. Re-Treatment Guidelines**

All patients who are randomized to receive study treatment on variable schedule dosing will be evaluated by the Study investigator every four weeks. Additional treatment is administered during follow-up visits if the Study-certified ophthalmologist determines that

treatment is warranted based on the guidelines below. The *minimal* interval between treatments may be 23 days.

Treatment is warranted if there are signs of active CNV. **It is anticipated that most re-treatment decisions will be driven by the presence or absence of fluid (subretinal, intraretinal fluid, or sub-RPE) on the OCT.** Eyes with fluid on OCT should be treated, with the exception of eyes in which there has been no decrease in fluid after three consecutive monthly injections. For such eyes, it is possible that continued treatment may be futile and the ophthalmologist and patient may choose to suspend treatment. Treatment may be reinstated in these eyes at a later visit if there is increased fluid (relative to the visit when treatment was stopped) on OCT.

If there is no fluid on OCT, but there are other signs of active CNV, the eye should be treated. These signs include new subretinal or intraretinal hemorrhage, persistent subretinal or intraretinal hemorrhage, decreased visual acuity relative to the last visit without another explanation, increased lesion size on fluorescein angiography relative to the last angiogram, or leakage on fluorescein angiography.

Fluorescein angiography is required at specific visits and may be used in deciding whether treatment is warranted. Fluorescein angiography may be obtained at other visits to aid in the decision on whether treatment should be applied. Fluorescein angiography may also be obtained when there is no fluid on OCT and the decision to treat is based on new subretinal or intraretinal hemorrhage or decreased visual acuity relative to the last visit without another explanation. All fluorescein angiography should be submitted to the CATT Fundus Photograph Reading Center.

Patients who present for a “non-scheduled” study examination may be retreated if they meet the above criteria for retreatment and at least four weeks have elapsed since the last study treatment (variable dosing schedule patients only.) If the patient is retreated, no additional intravitreal study treatment may be administered for the next 23 days.

#### **4.4. WITHHOLDING TREATMENT DUE TO POST-TREATMENT ADVERSE EVENT IN STUDY EYE – ALL TREATMENT GROUPS**

If a patient experiences a serious adverse event in the study eye after treatment, the Investigator may, at her/his discretion withhold additional treatment until the event has resolved. Such events in the study eye include, but are not limited to:

- intraocular inflammation  $\geq 2+$  (anterior chamber cells  $>10$  cells per  $\text{mm}^2$ )
- intraocular pressure  $\geq 30$  mmHG
- vitreous hemorrhage with a  $\geq 30$  letter loss in visual acuity
- new sensory rhegmatogenous retinal break or detachment (including macular hole)
- local infection

Refer to Exhibit 4-2 for more detailed definitions and procedures for withholding treatment for eyes with post treatment adverse events.

## **4.5. METHODS FOR ORDERING, HANDLING, AND STORING STUDY DRUG**

### **4.5.1. Methods for ordering, handling and storing Avastin®**

The CATT Investigational Drug Service (IDS) supplies kits for injections of Avastin®. Each kit will contain one filled **tuberculin syringe** and one 30-gauge x ½ inch injection needle for the intravitreal injection. Syringes are for single eye use only.

The initial supply of Avastin® is ordered by the Coordinating Center when a site has achieved CATT certification. Subsequent supplies are ordered by the clinic coordinator by faxing the Drug Re-Order Form to the IDS. Coordinators are encouraged to order as many kits as can be stored and used until the drug expires.

The IDS uses next day shipping and sends the designated drug recipient at the center information to track the package. The clinic coordinator must track packages not received by the following afternoon and the IDS needs to be immediately notified about lost shipments. The IDS ships the drug in a foam shipper with cold packs. The staff at each receiving site will inspect the conditions of each shipment of medication kits upon arrival, and immediately transfer the contents into appropriate, refrigerated storage locations. Kits received with warm or broken cold packs will be rejected, placed in quarantine, and the Drug Distribution Service notified. Study drug should be refrigerated at 2°-8°C (36°-46°F). **DO NOT FREEZE**. Do not use drug beyond the date printed on the packaging. Syringes should be protected from light. Store in the original carton until time of use. See Chapter 5.2.12 for requirements for record keeping. Unused or outdated syringes must be destroyed at the Clinical Center or returned to the Drug Distribution Center for destruction, as specified in the CATT Medication Manual and in Exhibit 4-3.

Study drug must be stored securely in the clinic (if a separate pharmacy is not used) or in the local or on-site pharmacy (if one is used). It is important that study drug is not accessible to non-study staff. If the medication must be stored in a refrigerator that is accessible to other staff, it is recommended that a separate locked box be used.

All medication kits received must be logged in and documented on the Avastin® inventory form. Similarly, each time Avastin® is dispensed to a CATT patient, it must be documented on the Inventory Log by affixing the tear-off portion of each syringe label on the Inventory Label indicating the patient's study ID number, alpha code and date dispensed.

### **4.5.2. Methods for handling and storing Lucentis®**

Staff at each clinical center will be responsible for obtaining Lucentis® for use in the Study. Procedures identical or similar to those used for non-Study patients should be used. In most centers, Lucentis® will be obtained from a center-affiliated pharmacy or from onsite supplies. Lucentis® should be refrigerated at 2°-8°C (36°-46°F). **DO NOT FREEZE**. Do not use beyond the date printed on the packaging. Vials should be protected from light. Store the vial and accompanying materials in the original carton until time of use.

Each time Lucentis® is dispensed to a CATT patient for study treatment, it must be documented on the Lucentis® Inventory Log distributed by the Coordinating Center or in a way that provides the same information as the Log. The information must include the lot number and expiration date (or vial label), the patient's study ID number, alpha code and date dispensed.

#### **4.5.3. Preparation of the syringe and maintaining masking of the CATT ophthalmologist**

The Clinic Coordinator is responsible for having the syringe presented in a masked manner to the CATT ophthalmologist. The Clinic Coordinator will obtain the drug to be injected from their local supply of each drug. For patients assigned to Lucentis®, the Clinic Coordinator, or another designated individual at the clinical center, fills a syringe, provided by the Coordinating Center to match the filled Avastin® syringes, as indicated in step 2 of Exhibit 4-1. For patients assigned to Avastin® the Clinic Coordinator, or another designated individual at the clinical center, attaches the needle for injection to the prefilled syringe, removes the IDS labeling from the syringe, and attaches the IDS label to the Avastin® inventory log. For all patients, the Clinic Coordinator, or another designated individual, labels the syringe with the words “CATT Study Drug”, along with the patient's ID number, alphabetic code and study eye. (Syringe labels are provided by the Coordinating Center.) The Clinic Coordinator presents the filled syringe to the CATT-certified ophthalmologist who will perform the injection. **The Clinic Coordinator, and the person filling the syringe if different from the Clinic Coordinator, may not reveal the content of the syringe to anyone else at the clinical center.** Timing and the exact steps performed by the Clinic Coordinator should be as similar as possible for the two study drugs. For example, if the time to acquire one drug is longer than the time required for the other drug, the Clinic Coordinator should adjust the time of delivering the syringe to the CATT ophthalmologist so that it is identical for the two drugs.

### **4.6. INTRAVITREAL INJECTION PROTOCOL**

#### **4.6.1. Administration**

The injection protocol used in the Trial has been adapted from the protocol developed by the Diabetic Retinopathy Clinical Research Network (DRCRnet) and from the Lucentis® preparation guidelines (Genentech, Inc. 2006). Procedures will be implemented to minimize the risk of potential adverse events associated with serial intraocular injections (e.g., endophthalmitis). Aseptic technique must be observed by clinic staff involved in the injection tray assembly, anesthetic preparation and administration, and study drug preparation and administration. In addition to the procedures outlined in the protocol, added safety measures in adherence to specific institutional policies associated with intraocular injections should be observed.

Study drug will be administered in the study eye only. Intravitreal injection must be performed by the CATT-certified ophthalmologist following a slit lamp examination. See Exhibit 4-1 for detailed pre-injection procedures.

The needle of the syringe containing 50 µL of study drug solution will be inserted through the pre-anesthetized conjunctiva and sclera, approximately 3.0–4.0 mm posterior to the



limbus, avoiding the horizontal meridian and aiming toward the center of the globe. The injection volume should be delivered slowly. The needle should then be removed slowly to ensure that all drug solution is in the eye. (See Exhibit 4-1 for detailed instructions for administration.)

At the discretion of the ophthalmologist, antimicrobial drops may be administered immediately following the intraocular injection or may be self-administered by the patient four times daily for 3 days following each intraocular injection.

#### **4.7. POST ADMINISTRATION SAFETY TELEPHONE CALL**

Clinic Coordinators telephone the patients 3-5 days after the first intraocular injection to assess whether the patient has experienced an adverse effect(s) of treatment. If the coordinator believes that such an event may have occurred, the patient is asked to return to the Clinical Center immediately for an evaluation. Patients with complications are treated according to best medical judgment.

#### **4.8. TREATMENT DISCONTINUATION BECAUSE OF ADVERSE EVENTS**

Exhibit 4-2 lists recommended criteria to guide clinical decision-making. Should any of the events in Exhibit 4-2 occur, and the managing ophthalmologist decides to withhold treatment, the reason should be recorded on the Treatment Evaluation Form for the visit and, if applicable, on the Adverse Event Log.

#### **4.9. PRIOR AND CONCOMITANT THERAPY**

Patients with previous treatment for CNV in the study eye are excluded from the Study. However prior treatment for CNV in the non-study eye is NOT an exclusion and will be documented on study forms. Concomitant treatment with Lucentis<sup>®</sup>, Avastin<sup>®</sup> and non-investigational agents is allowed. At all follow-up visits, patients will be asked about any additional treatments for any ocular condition, in either the study or non-study eye.

##### **4.9.1. Concomitant Therapy for the Study Eye**

No other treatment for choroidal neovascularization should be given to the study eye, including, but not limited to, laser photocoagulation, photodynamic therapy, Macugen<sup>®</sup> therapy, transpupillary thermotherapy, external beam radiation therapy, submacular surgery, or other surgical intervention for AMD. No other experimental or investigational treatments are permitted during this study; this includes ocular experimental and investigational treatments in the study eye (see Section 3.2.1).

Elective vitrectomy surgery is not allowed in the study eye during study participation. Onset of glaucoma during study participation should be treated as clinically indicated. Cataract surgery in the study eye may be performed if clinically indicated and should occur > 30 days after the previous study injection; the next study injection will be held for  $\geq$  30 days following cataract surgery.

If patients choose to discontinue their Study treatment in favor of an alternative treatment for choroidal neovascularization, certain precautions must be taken. If an anti-VEGF

agent is to be administered, treatment must not be initiated in the study eye < 23 days following the last Study treatment.

#### **4.9.2. Concomitant Therapy for the Non-Study Eye**

Treatment of CNV that develops in the non-study eye during the follow-up period should follow the best medical judgment for the patient. Every effort should be made to decide on the treatment for the non-study eye without unmasking the CATT ophthalmologist managing the patient. Possible treatments include thermal laser, photodynamic therapy, Macugen<sup>®</sup>, Lucentis<sup>®</sup>, or Avastin<sup>®</sup>. Other investigational agents should not be used for treatment of the non-study eye.

#### **4.9.3. Follow-up of Patients Who Have Discontinued Lucentis-Avastin Trial Study Treatment**

Patients who discontinue treatment will continue to be followed in the Study. Collecting data about the follow-up status of the eyes of patients who discontinue treatment is crucial in fully evaluating the treatment groups. If treatment is discontinued due to concomitant therapy or treatment related adverse events in the study eye, patients are expected to complete follow-up visits and undergo visual acuity testing, OCT, color photography and fluorescein angiography as specified for their treatment group in this protocol.

#### **4.10. MANAGEMENT OF PATIENTS WHO DEVELOP INJECTION-RELATED COMPLICATIONS**

Complications that arise from study treatment (e.g. endophthalmitis following an intravitreal injection) will be treated according to best medical judgment.

## EXHIBIT 4-1

### LUCENTIS-AVASTIN TRIAL INTRAVITREAL INJECTION PROCEDURES

The following procedures will be implemented to minimize the risk of potential adverse events associated with serial intravitreal injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. In addition to the procedures outlined below, added safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The injection protocol used in Lucentis-Avastin Trial is the protocol developed by the Diabetic Retinopathy Clinical Research Network (DRCRnet), with the specific injection volume and needle gauges adjusted for injection of Lucentis® or Avastin® in this study. The following procedures (except where noted) will be performed by a CATT-certified treating ophthalmologist.

#### 1. Pre-Injection

- a. On the day of injection, topical antibiotic drops may be administered at the discretion of the investigator.
- b. When the patient is ready for the injection, apply a drop of topical anesthetic to the eye.
- c. Additional anesthesia will be at the discretion of the investigator but the use of lidocaine gel is not recommended since the gel may interfere with the action of povidone iodine. Additional anesthesia may include application of a cotton-tipped applicator soaked in topical anesthetic over the intended injection site, use of a subconjunctival anesthetic including subconjunctival lidocaine, etc.
- d. The eye will then be prepared for injection using one of the following sequence of steps:
  - Place 2-3 drops of 5% povidone iodine in the lower fornix. (Optional: Using sterile cotton-tipped applicators soaked in 5% povidone iodine, scrub the upper and lower eyelid margins and the upper and lower eyelashes.)
  - Place a sterile eyelid speculum to stabilize the eyelids.
  - A cotton-tipped applicator soaked in 5% povidone iodine is applied to the conjunctiva directly over and surrounding the intended injection site. Encourage the patient to look superonasally during the application of 5% povidone iodine to the intended injection site. Allow 30-60 seconds for the povidone iodine to dry before injection.

OR

- Place a sterile eyelid speculum to stabilize the eyelids.
- Apply either a cotton-tipped applicator soaked in 5% povidone iodine or a 10% povidone iodine Swabstick directly over the intended injection site. Encourage the patient to look superonasally during the application of povidone iodine to the intended injection site. Allow 30-60 seconds for the povidone iodine to dry before injection.

## EXHIBIT 4-1 (continued)

OR

- A 5% povidone-iodine flush can be performed. Start by using a sterile needle to draw up at least 10cc of 5% povidone-iodine into a syringe. Following this, the needle should be discarded and a sterile angio-catheter should be attached to the syringe and used for irrigation. If desired, the catheter tubing may be trimmed using sterile scissors. Next the fornices and the caruncle should be irrigated with at least 10 cc of 5% povidone-iodine using a forced stream from the angio-catheter.
- Place a sterile eyelid speculum to stabilize the eyelids.

OR IF THE PATIENT IS ALLERGIC TO IODINE

- Apply one drop of topical antibiotic every 5 minutes for 3 doses prior to injection.
- Place a sterile eyelid speculum to stabilize the eyelids.

### 2. Filling the Syringe for Patients Assigned to Lucentis®

- a. Disinfect the rubber stopper on the vial of study drug with isopropyl alcohol. Disinfect hands.
- b. Aseptically attach the 1½ inch needle onto the syringe, and carefully remove the needle cap.
- c. Insert the sterile needle through the center of the stopper and draw the entire contents of the vial into the syringe.

### 3. Attaching the Injection Needle

- a. For patients assigned to Lucentis®, remove the 1½ inch needle used to draw up the drug. For patients assigned to Avastin®, remove the luer tip cap.
- b. Place the sterile 30-gauge, ½ inch needle onto the syringe. Fluid is expelled at an approximately 45-degree angle over a sterile surface until the plunger is advanced to 50 µL. The syringe is now ready for injection.

### 4. Injection

- a. Sterile calipers or the blunt end of a sterile Tuberculin syringe (diameter equal to approximately 4.0mm) are used to locate the position of the injection site. The entry site for the intravitreal injection should be 3.0mm-4.0mm posterior to the limbus.
- b. Inject the study drug into the vitreous cavity pointing toward the optic nerve via the pars plana.

### 5. Post-Injection

- a. Remove the lid speculum and avoid any excess pressure on the eye.
- b. Indirect ophthalmoscopy is performed to confirm that the central retinal artery is perfused and to assess any complications.

**EXHIBIT 4-1 (continued)**

- c. At the discretion of the investigator, a bottle of topical antibiotic may be provided to the patient and used QID for 3 days (inclusive of the day of injection).

***NOTE: The patient should not be permitted to leave the physician's office until perfusion of the central retinal artery is confirmed. IOP may be checked  $\geq 10$  minutes after injection. The last IOP taken before the patient leaves the physician's office should be recorded.***

## EXHIBIT 4-2

### TREATMENT DISCONTINUATION CRITERIA DUE TO ADVERSE EVENTS IN THE STUDY EYE

<b>Event in Study Eye</b>	<b>Drug Dose-Holding Criteria</b>
Intraocular inflammation	Hold dose if intraocular inflammation is $\geq 2+$ (anterior chamber cells $>10$ cells per $\text{mm}^2$ ) in the study eye).
Intraocular pressure	Hold dose if intraocular pressure in the study eye is $\geq 30$ mmHg. Treatment will be permitted when intraocular pressure has been lowered to $< 30$ mmHg, either spontaneously or by treatment, as determined by the Investigator.
Vitreous hemorrhage	Hold dose if there is a vitreous hemorrhage sufficient to produce a $\geq 30$ -letter decrease in visual acuity in the study eye compared with the last assessment of visual acuity prior to the onset of the vitreous hemorrhage. Treatment will be permitted when the vitreous hemorrhage improves to allow a visual acuity score improvement to a $< 30$ -letter decrease.
Sensory rhegmatogenous retinal break or detachment (including macular hole)	Hold dose if a new retinal break is identified in the study eye. Treatment may be resumed $\geq 23$ days after the retinal break has been successfully treated.
Local infection	Hold dose if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis or endophthalmitis in either eye.

The ophthalmologist may discontinue a patient from additional treatment for other safety reasons if in the best medical judgment of the treating ophthalmologist it is believed that there is no chance of any benefit to the patient from additional intravitreal injections in terms of preserving vision or retinal anatomy.

## EXHIBIT 4-3

### ***Returning or Destroying Expired or Damaged Drug***

Expired or Damaged drug can either be destroyed on-site, or shipped back to the coordinating center pharmacy (IDS). The same form is used in both cases, and the inventory log must be updated. Do this as follows:

1. Contact the IDS and ask for a Destruction/Return Form. This will be faxed or emailed to you.
2. Document the # of syringes and the reason.
3. Fill in the lot # and use-by date.
4. Sign the form.
5. **If destroying on-site**, fax the form back to the coordinating center pharmacy (IDS) and keep the original in your study records. Acceptable methods of destruction include incineration, yellow-bag (chemotherapy) waste or red-bag (biohazard) waste. If your site uses a different method than these, contact the central pharmacy to discuss and determine if your method is acceptable.
6. **If sending back**, pack the syringes/kits well (sealed plastic bag to catch leaks, and bubble wrap or foam peanuts to prevent breakage). Send ambient (room temperature) along with a copy of the form. Keep the original in your study records.
7. On the inventory record, enter the quantity you removed from inventory, and enter the new balance. Hand-write the lot # and use-by date of the syringes you removed from inventory.

Note that the empty packaging does not need to be saved, as long as the tear-off label from the syringe is properly affixed to the inventory record and the inventory record is properly completed.

## CHAPTER 5

### PATIENT VISITS AND EXAMINATIONS

#### 5.1. INTRODUCTION

Each patient enrolled in the Study is required to have study visits at the CATT clinical center every four weeks through the first 104 weeks (2 years) (See Exhibit 5-1). Patients are enrolled in the Trial, randomized to one of four treatment groups and treated in one eye during one or more encounters comprising a baseline visit. Patients assigned to either the Lucentis<sup>®</sup> on fixed schedule group or the Avastin<sup>®</sup> on fixed schedule group will be re-randomized at 52 weeks either to continue following a fixed schedule of injections every 4 weeks or to follow a variable dosing schedule.

Activities to be completed at each follow-up visit are specified in Exhibit 5-1 and vary by treatment group (fixed schedule vs. variable). At least one Study data collection form must be completed documenting each of the required visits.

Study patients may be seen in the clinical center between their regularly scheduled visits. Patients are encouraged to call the Clinic Coordinator at any time a decrease in vision is noticed so that the patient may be scheduled for an examination in the clinical center to assess the cause of the decrease in vision. Alternatively, the Study Investigator may believe that examining the patient more frequently than required by the Study schedule is in the patient's best interest. No data collection forms are required for these extra visits unless the investigator determines that additional treatment is required. However, study treatment may not be administered any more frequently than once every 23 days.

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 submitted to the Web based CATT data system.

#### 5.2. PRE-ENROLLMENT PROCEDURES

Pre-enrollment procedures encompass the activities of evaluating the patient for eligibility by performing visual acuity testing, fundus photography, fluorescein angiography, OCT, an ophthalmological examination, and by questioning the patient about concurrent conditions. The order in which these procedures are performed may vary from clinic to clinic, subject to the restrictions discussed below. All procedures must be completed within 7 days prior to randomization.

##### 5.2.1. Patient Identification

Each patient will be assigned a permanent identification number and alphabetic code to be used on all study forms, photographs and OCTs. The patient identification number is a two-part identifier consisting of a two-digit clinic number and three-digit sequence number. Patients will also have a four-letter randomly generated alphabetic code that is not linked to their name. The patient identification number and alpha code are available on pre-printed patient registration logs.



Each patient is also associated 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. The patient's identification number and alphabetic code are permanent and do not change even if a patient is transferred.

### **5.2.2. Informed Consent**

Informed consent must be obtained before the patient undergoes Study-specific procedures. Specifically, if the procedures used routinely in the clinical center for OCT, photography, refraction, or visual acuity testing are not identical to those specified by the CATT protocol, then consent **MUST** be obtained prior to the performing the procedure. The Coordinating Center has distributed a script (Exhibit 13-2) to the Clinical Centers that may be used to obtain patient consent for conducting screening studies prior to obtaining the patient's consent to participate in the full study. Clinical Centers may use this script with the approval of the local IRB. The Clinic Coordinator and the enrolling CATT Ophthalmologist share responsibility for the patient's orientation into the Study, 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 ensure that all of the patient's questions and those of the family are answered satisfactorily. The patient should not be asked to sign the consent form until either the Clinic Coordinator or the CATT Ophthalmologist has answered all questions. It is important that the patient understands the concept of randomization in clinical trials.

If the patient is not ready to sign the consent form during the baseline visit, the patient may go home to think about enrolling in the trial. All parts of the baseline visit must be completed within 7 days prior to randomization. Before information is submitted to the CATT Web-based Data Entry System, a patient must sign the consent form.

### **5.2.3. Patient History**

The Clinic Coordinator and Ophthalmologist, as appropriate, should review with the patient those questions on the Baseline General Information Form, Baseline Medical History Form and Assessment of Eligibility Form that can be answered prior to ophthalmoscopy and photography to ensure that the patient is eligible. Participation in other clinical trials is not an automatic exclusion; however, the Clinic Coordinator must call the Director of the Coordinating Center to discuss the treatment and follow-up required for any study in which the patient is already participating. If the patient is participating in the AREDS2 study, it should be noted on the form but the Clinic Coordinator does not need to contact the Coordinating Center.

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.

### **5.2.4. Testing Visual Acuity**

Refraction and testing of visual acuity to fulfill study eligibility criteria must be performed before the patient's eyes are dilated and before fundus photography and OCT if these procedures are to be

carried out on the same day. Refraction must precede visual acuity testing. If the Clinic Coordinator is also certified as a Refractionist and Visual Acuity Examiner, the Clinic Coordinator may perform the refraction and visual acuity during the baseline visit only. Standardized procedures as described in Chapter 7 must be followed. The Coordinator cannot refract the patient or test visual acuity during follow-up visits.

### **5.2.5. Ophthalmological Examination**

A Study-certified 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.

### **5.2.6. Fundus Photography**

A Study-certified Photographer takes mydriatic stereoscopic color photographs and a fluorescein angiogram of both eyes according to the standardized procedures described in Chapter 8. Photography must be performed after testing visual acuity if these procedures are carried out on the same day.

### **5.2.7. Optical Coherence Tomography (OCT)**

An OCT of both eyes is taken by a Study-certified OCT Technician according to the standardized procedures described in Chapter 9. Because the eye must be dilated for OCT, it must be performed after testing visual acuity if these procedures are carried out on the same day.

### **5.2.8. Use of Medications and Dietary Supplements**

The Clinic Coordinator must complete a Baseline Concomitant Medication Form to indicate if the patient currently takes medications or dietary supplements. If they do, the appropriate forms must be completed prior to enrolling and randomizing the patient.

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

All procedures involved in the baseline visit must be performed within a 7-day period preceding the randomization. Thus, if the OCT, color photographs, the fluorescein angiogram, or visual acuity testing are more than 7 days old on the day that the patient is to be randomized, the procedure(s) must be repeated.

After the Ophthalmologist assesses from photography, ophthalmic examination, OCT, visual acuity testing and medical history that the patient is eligible for the trial and if the patient has signed a consent form, the Clinic Coordinator will enter the data into the CATT Data Management system. (See Section 5.8 for information on submitting data to the CATT Data Management System.) The data system will check all entered responses against all eligibility criteria and will indicate which items, if any, need correction or confirmation. If all required data have been received and the patient is eligible, the Clinic Coordinator opens a form, answers questions about data collection completeness, and saves the form to generate a randomized treatment assignment for the patient. The system will then generate a report that provides the treatment to which the patient has been assigned. The Coordinator will print the treatment assignment report and the follow-up visit schedule. The baseline visit materials and follow-up visit schedule are filed in the

patient's Study chart. The treatment assignment screen should be filed with the Patient Log in a notebook and kept in a locked cabinet.

#### **5.2.10. Re-Randomization of Patients Assigned to the “Fixed Treatment” Group**

At 52 weeks, patients assigned to either of the two fixed schedule treatment groups will be randomized again to either continue with the fixed dosing schedule or to begin a variable dosing schedule for the next year. The study medication will not change from the original assignment of Lucentis<sup>®</sup> or Avastin<sup>®</sup>. This will be done by the clinic coordinator submitting the patient's ID number to the Web-based CATT data management system and requesting a 52-week randomized assignment. After confirming that the patient was previously randomized to a fixed schedule treatment group, the system will issue the treatment assignment for the next year. If the week 52 visit is missed, the re-randomization procedure can occur at any time after the visit window has closed.

#### **5.2.11. Masking to Treatment Assignment**

There are different levels of masking within the study. The Refractionist and Visual Acuity Examiner are masked to the treatment assignment (study drug and dosing schedule) for all follow-up visits. The Ophthalmologist knows the dosing schedule but is masked to whether the patient is receiving Lucentis<sup>®</sup> or Avastin<sup>®</sup>. The Clinic Coordinator is unmasked to both the study drug and dosing schedule. Patients are initially masked to the study drug but may find out the identity of the drug from billing documents. To ensure that the Ophthalmologist remains masked to the study drug assigned to the patient, an important task of the Clinic Coordinator is to remind the patient not to discuss the drug they are receiving with the Ophthalmologist. Similarly, patients (and clinic staff) must be reminded not to discuss the dosing schedule or drug received with either the Refractionist or Visual Acuity Examiner prior to each examination.

All personnel in the CATT Fundus Photograph Reading Center and the CATT OCT Reading Center will be masked to whether the patient is receiving Lucentis<sup>®</sup> or Avastin<sup>®</sup>.

#### **5.2.12. Medication and Record Keeping**

During the randomization process, each participant is assigned to receive either Lucentis<sup>®</sup> or Avastin<sup>®</sup>. The study supplies the Avastin<sup>®</sup> through the Drug Distribution Service. Lucentis<sup>®</sup> is purchased and stored by the clinical center in a manner identical to its use outside of the study (i.e., standard practice).

If the patient is assigned to Lucentis<sup>®</sup>, the Clinic Coordinator will obtain a box of Lucentis<sup>®</sup> from the practice inventory. Using the 19 gauge filter needle provided in the Lucentis<sup>®</sup> packaging, the Clinic Coordinator will draw up the medication into a syringe provided by the Coordinating Center to match the Avastin<sup>®</sup> syringes and then attach a 30 gauge injection needle. The Clinic Coordinator will affix to the syringe a label with the patient's ID number, alphabetic code and study eye and give it to the Ophthalmologist to administer treatment. The dispensed vial must be recorded on the Lucentis<sup>®</sup> Inventory Log or similar document by the Clinic Coordinator.

If the patient is assigned to Avastin<sup>®</sup>, the Clinic Coordinator will obtain a package consisting of a single use medication syringe supplied by the Investigational Distribution Service. The Clinic Coordinator will attach a 30 gauge injection needle. The Clinic Coordinator will remove the IDS

label from the syringe and affix it to the Avastin<sup>®</sup> Inventory Log. The Clinic Coordinator will then affix to the syringe a label with the patient's ID number, alphabetic code and study eye and give it to the Ophthalmologist to administer treatment.

Federal law requires documentation of receipt, use, and disposition of every dose of investigational medication. The CATT Drug Distribution Center has the responsibility to assure the FDA that systems for medication accountability are being maintained by investigators at the Clinical Centers. To assist in fulfilling these requirements, a set of drug accountability records has been prepared for use by each site.

A Drug Accountability Log is supplied to simplify the accountability of the study-supplied Avastin<sup>®</sup> from receipt to return/destruction of unused product. When study-supplied Avastin<sup>®</sup> is used for treatment, the date of treatment and initials of the individual dispensing the drug are recorded. Finally, when medication is returned to the CATT Investigational Drug Service or destroyed on site, there is a place to record this as well. Medication Dispensing Logs for Lucentis<sup>®</sup> are also supplied to record the use of Lucentis<sup>®</sup> for each CATT treatment.

### **5.2.13. Treatment**

Patients and CATT-certified Ophthalmologists should be prepared to commence treatment to the study eye immediately after randomization. (See Chapter 4.6 for the detailed treatment protocol.) An Intravitreal Injection Treatment Form is completed using information provided by the treating Ophthalmologist. Before the patient leaves the clinical center, the Clinic Coordinator schedules a time to call the patient to conduct a short safety telephone call 3-5 days later and schedules the patient's next study visit in four weeks.

## **5.3. SAFETY CHECK TELEPHONE CALL**

A safety check telephone call is scheduled for 3-5 days after the first study injection. The Clinic Coordinator should schedule this telephone call with the patient prior to the patient leaving the office after the first treatment. The purpose of the call is to assess whether or not the patient has experienced an untoward effect of the study injection and address concerns that the patient may have. A brief form is completed to document the telephone call and is entered into the CATT database by the Clinic Coordinator. Documentation of the telephone call is also recorded in the patient's medical record and signed and dated by the clinic coordinator.

## **5.4. REGULARLY SCHEDULED FOLLOW-UP VISITS THROUGH 104 WEEKS**

Follow-up visits are scheduled every four weeks for a total of 104 weeks (2 years after enrollment into the Study).

### **5.4.1. Preparing for Follow-Up Visits**

The following tasks should be performed before the patient arrives for a scheduled follow-up visit.

- Remind the patient of the scheduled appointment by telephone or by mail in advance of the date.
- Retrieve the patient's Study file.

- Log onto the CATT database and print a packet of all forms and logs required for the specific follow-up visit. Each page of the printed forms will be pre-populated with the patient's Study identification number, alphabetic identification code, and visit code. When printing forms for each visit, the clinic coordinator must remember to print the Concomitant Medication Log and Adverse Event Log located in separate “tabs” in the CATT database. In the rare event the system cannot print the forms required for the visit, the clinic coordinator will photocopy the forms from the Forms Notebook resident at the site and must label each page with the identifying information.
- Be sure that any pertinent information received since the last examination is available to the investigators.
- Put the Patient Information Form in the folder as a reminder to review and update the information.

#### 5.4.2. Follow-Up Visit Procedures

The procedures to be performed at each follow-up visit are displayed in Exhibit 5-1. Patient history, visual acuity testing, ophthalmological examination, and evaluation for treatment are performed at every visit. Treatments are performed on a fixed or variable dosing schedule. As during the baseline visit, visual acuity testing must be performed before dilation of pupils, and OCT testing and ophthalmological examination after dilation of pupils. Photography is performed in both eyes at weeks 052 and 104 at sites that do not participate in the fluorescein substudy; at sites participating in the fluorescein substudy, photography is performed in both eyes at weeks 012, 024, 052 076 and 104. OCT is performed at weeks 004, 008, 012, 024 052, 076 and 104 for the patients in the fixed schedule group; OCT is performed at every visit for patients in the variable dosing schedule groups.

**Assessing Interim Medical History During Follow-up Visits:** The CATT General Follow-Up Visit Form specifies collection of data from the patient regarding their health, medications, vision, other ocular treatments, and possible adverse events (AEs) since the patient’s last Lucentis-Avastin Trial visit. All AEs must be recorded on the AE Log. If the investigator identifies an adverse event as serious, it must also be reported to the Coordinating Center on the CATT Serious Adverse Event Reporting Form as detailed in Section 6.9 of this manual. Either the Clinic Coordinator or Study Ophthalmologist may ask the patient these items. Visual Acuity Examiners are never to ask these items as the patient’s response may jeopardize the Visual Acuity Examiner’s masking to treatment schedule and study medication. If additional or follow-up information is obtained about a previously reported serious adverse event, the Clinic Coordinator or Ophthalmologist must complete a SAE Follow-Up Reporting Form.

**Visual Acuity Testing:** A certified Visual Acuity Examiner must perform the standardized, e-ETDRS visual acuity testing (Chapter 7). To minimize potential bias, the Clinic Coordinators may not perform visual acuity testing during follow-up visits. The Clinic Coordinator should supply the Visual Acuity Examiner with the patient’s record of subjective refraction from the previous test. In the rare occurrence of a malfunctioning e-ETDRS system, the coordinator should provide the Visual Acuity Examiner with the paper ETDRS Chart Worksheet to record the results of visual acuity testing.

**Refraction:** Refraction is required only at follow-up visits for which the visual acuity score will be used to evaluate treatment efficacy (see Exhibit 5-1). A CATT-certified Refractionist must perform the standardized, e-ETDRS refraction (Chapter 7). The Clinic Coordinator may not perform refraction during follow-up visits.

**Fundus Photography:** Fluorescein angiography and color photography of the study eye are required as specified in Exhibit 5-1. A CATT certified photographer takes mydriatic stereoscopic color photographs and a fluorescein angiogram according to the standardized procedures described in Chapter 8. Photography must be performed after testing visual acuity if these procedures are carried out on the same day. If not performed on the same day, photography must be performed within 7 days of the visual acuity test.

**Patient Information:** At all follow-up visits, 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.

#### **5.4.3. Follow-Up Visit Procedures if the Week 52 Visit is Missed**

Because the primary outcome of the CATT study is visual acuity at one year, a missed visit at week 52 has a greater negative impact on CATT results than when other visits are missed. If the week 52 visit is missed, a protocol refraction, visual acuity testing, OCT, fundus photographs and angiography must be completed for all patients at the next completed study visit that occurs within the week 56, 60 or 64 visit window. In addition, if the patient is assigned to fixed monthly treatments, you must re-randomize the patient prior to evaluating the need for treatment.

Data collected at these visits must be entered in the visit week during which the testing actually occurred (e.g., if you are testing visual acuity at week 60 enter the data in the week 60 tab). Do NOT enter the data in week 52 if the visit occurred outside of the week 52 visit window. The exception to this is the re-randomization (RAND2) form, which resides on the week 52 visit tab and must be completed there.

#### **5.4.4. Study Treatment During Follow-up Visits**

##### **Fixed Schedule Lucentis<sup>®</sup> and Avastin<sup>®</sup> Patient Groups**

All patients assigned to fixed schedule group will receive additional study treatment during each study visit, unless a contraindication to injection develops (see Exhibit 4-2) or unless the ophthalmologist believes that additional treatment is futile (see section 4.2.1). Results of the OCT, visual acuity testing, and fluorescein angiogram (if performed) will not affect treatment decisions.

##### **Variable Schedule Lucentis<sup>®</sup> and Avastin<sup>®</sup> Patient Groups**

Patients who are assigned to treatment with either variable schedule Lucentis<sup>®</sup> or Avastin<sup>®</sup> will receive additional treatment if there are signs of lesion activity and no contraindication to injection has developed. See Section 4.3.2 for guidelines on retreatment decisions. If a fluorescein angiogram was done to aid the ophthalmologist in his/her determination of the need for additional treatment, the angiogram must be submitted to the Fundus Photograph Reading Center.

#### **5.4.5. Study Treatment During “Non-Regularly Scheduled” Study Visits (Variable Schedule Patients Only)**

There may be times when a Study patient returns to the Clinical Center before their next regularly scheduled study visit, either because the Study Ophthalmologist wishes to re-examine the patient sooner than in 4 weeks or because the patient reports symptoms. During these “non-scheduled” visits, the Study Ophthalmologist may decide that the patient should be retreated if at least 23 days have elapsed since the prior study treatment (variable dosing schedule patients only.) If the patient is retreated, he/she cannot be treated again at their next scheduled study visit if the next visit occurs sooner than 23 days later.

#### **5.4.6. Reporting Adverse Events**

All adverse events (AEs) that occur from the time the patient enrolls into the Lucentis-Avastin Trial through the end of the study follow-up period must be reported. The Clinic Coordinator is responsible for entering the AE data into the Web-based system. If a Serious Adverse Event (SAE) occurs, the Clinic Coordinator is responsible for submitting the SAE Reporting Form to the CATT Coordinating Center and for submitting a SAE report to the local IRB (if required by local IRB rules). If additional information is obtained on a serious adverse event that was previously reported it must be reported on the SAE Follow-Up Reporting Form. (See Chapter 6 for a detailed discussion on reporting adverse events.)

#### **5.4.7. Scheduling Required Visits and Procedures**

It is extremely important that both the Clinic Coordinator and the patient adhere to the follow-up appointment schedule. The patient's appointment 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 visit should be scheduled as close as possible to the target date. Whenever a visit is completed near the end of a time window, an attempt should be made to get the patient back on schedule. Visits not completed within the specified time limits are classified as missed.

The Clinic Coordinator plays a crucial role in ensuring that the required procedures and visits occur on schedule. Before the patient leaves the Clinical Center, the Clinic Coordinator schedules the next visit. Thus, whenever a patient leaves a Study visit, he/she should have an appointment card with the date of the next visit.

When scheduling each study visit, the Clinic Coordinator should consult the “Required Study Visits and Visit Procedures” chart (Exhibit 5-1) to ensure that all requisite tests are scheduled.

#### **5.4.8. Follow-up of Patients Unable to Return for Scheduled Visits**

Because of poor health or for other reasons, some patients may not be able to return to the Clinical Center for scheduled study visits despite their original intentions to do so. Information regarding unresolved SAEs can be obtained by the Clinic Coordinator through telephone calls or, after obtaining patient consent, records from a non-study physician whom the patient has seen may be obtained. If the patient cannot be located through family members or friends, a Patient Search Form should be initiated. Coordinators must still complete Missed Visit Forms for these patients.

If the Clinic Coordinator discovers that the patient has died, the Clinic Coordinator follows procedures for reporting a serious adverse event and completes a Patient Death form in the Web-based CATT system.

#### **5.4.8.1. Missed Visits**

Any time a patient misses a scheduled visit, the Clinic Coordinator should contact the patient immediately and arrange another appointment. Whenever it is not possible to examine the patient in a CATT Clinical Center, the following procedures should be followed to provide as much useful information as possible.

- If a Study patient cannot complete a scheduled visit within the time window for that visit, the Coordinating Center should be notified by completion and entry of a Missed Visit Form within one week of the close of the visit window.
- The patient should be contacted by telephone to schedule the next visit or to confirm the appointment for the next visit.
- The patient should be asked whether they have been examined during the time period covered by another ophthalmologist. If so, the name(s) of the other physician(s), 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 physician(s) to provide information on the patient.

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. Missed visit forms must be completed for these patients for each visit the patient missed.

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

During the course of their follow-up, some patients may choose to be seen at another CATT-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 study chart should be transferred to the new site.

Patients may move to another area of the country. If another CATT clinical center is located closer to the patient's new home, a permanent transfer may be arranged and documented with a Transfer of Patient Form. The CATT 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 from both clinics must sign the form indicating approval of the transfer, and fax the completed form to the Coordinating Center. The clinic at which the patient was originally enrolled should copy the patient's study chart and send it to the receiving clinic.



## **5.6. PATIENT DEATH**

As soon as clinic personnel become aware that a patient has died, the Clinic Coordinator follows procedures for reporting a serious adverse event, requests a death certificate, completes a Patient Death form, and enters the form into the CATT Web-based data system. The patient will then be removed from later reminders for visits.

## **5.7. GUIDELINES FOR DOCUMENTATION OF LUCENTIS-AVASTIN TRIAL ACTIVITIES**

In accordance with good research practice, it is essential that all study patient-related activities be documented so that information at the clinical centers can be compared with the data in the trial database and in source documents by study site visitors and/or outside auditors as necessary.

Information should be included that documents the following information:

- That all reported procedures and tests were conducted according to protocol.
- That all procedures and examinations were performed by the reported personnel on the dates reported.
- That the reported treatment regime was administered and explained to the patient per protocol by the specified personnel or that protocol deviations have been reported.

In addition to Lucentis-Avastin Trial 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.

### **5.7.1. 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 lab reports
- 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 Trial.

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 study 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 study charts.

### **5.7.2. Maintaining the Patient's Lucentis-Avastin Trial File**

All study visit materials are filed in the patient's study chart as is a copy of the follow-up appointment schedule. The following things should be done to keep the patient's study file as complete and up-to-date as possible at all times:

- The patient's contact information, 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 visit. Contacts already listed should be confirmed. If any changes are made, the information should be added to the Patient Information Form.
- Be sure that copies of the forms and all other information submitted to the CATT Coordinating Center and Reading Centers are in the patient's file.

## **5.8. SUBMISSION OF VISIT DATA TO THE CATT RESOURCE CENTERS**

One major responsibility of the Clinic Coordinator is to gather the data obtained at the study visit and submit it to the Coordinating Center, OCT Reading Center and (if necessary) to the Fundus Photograph Reading Center. Study forms should be entered in to the data system as soon as possible after the visit; forms entered more than 7 days later will be considered late. Photographic materials and OCTs should be submitted to the respective Reading Centers according to the procedures discussed in Chapters 8 and 9 of this manual.

The Clinic Coordinator should carefully check all data collection forms before entering the data in the web-based CATT data system. This process is extremely important because correcting errors that have entered the 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 initial or sign the appropriate component of the form, as indicated on the forms.

### **5.8.1. Entering Data into the On-Line Patient Enrollment and Randomization System**

At any point after the patient has signed a patient consent form, the Clinic Coordinator may enter baseline data into the on-line system in real time. For example, the Clinic Coordinator may enter the results of the OCT and visual acuity testing before the interpretation of the fluorescein angiogram is made.

The first step in entering data for a patient is to complete a Patient Registration Form. This form may be completed after the patient consent form has been signed. More information on entering data may be found in the CATT Database Management System Manual.

### **5.8.2. Submission of Data to the OCT Reading Center**

All patients enrolled in the trial are required to undergo OCT at the baseline visit and as specified in Exhibit 5-1. The results of the scans will be interpreted by the OCT Reading Center. The Clinic Coordinator has the responsibility to send the scan output to the OCT Reading Center, as specified in Chapter 9.

### **5.8.3. Submission of Photographic Materials to the Fundus Photograph Reading Center**

All patients enrolled in the trial are required to undergo photography (color photographs and fluorescein angiography) at the baseline visit and as specified in Exhibit 5-1. The results of the images will be interpreted by the Fundus Photograph Reading Center. The Clinic Coordinator has the responsibility to send the photographic images to the Fundus Photograph Reading Center, as specified in Chapter 8.

### **5.8.4. Completeness of Submitted Data**

Each data form should be checked for completeness and to assure that all pages of all components are included and in the correct order. In addition, the clinic coordinator should check the data screen before saving the data into the database. Data will be validated during the entry process. Whenever there is doubt about how an item is to be answered, the Protocol Monitors or Director at the CATT Coordinating Center 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 and data entry screen.

### **5.8.5. Consistency**

Questions that should be answered only for certain patients appear in boxes in the right hand column of each page of each form and data entry screen. An arrow leading from a specific response to a box indicates that whenever that response 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 are entered into the database.

## **5.9. EDITS AND CORRECTIONS**

### **5.9.1. Edit Queries**

The information submitted to the CATT database is edited for anomalies by means of special computer programs. When a question exists regarding the answer to one or more of the items on a component, the item is flagged by the data system. The Clinic Coordinator should first check for a data entry error by comparing the response on the paper copy of the form against the database response. If the edit query is due to a data entry error, the Clinic Coordinator may immediately correct the error. If the edit query is not due to a data entry error, the Clinic Coordinator should refer to the patient's record and determine the correct answer for each item flagged. The Clinic Coordinator may need to consult with the physicians or other technical staff for specific medical information. In this case, whenever a correction to an earlier value on the paper form is required, the Clinic Coordinator corrects the earlier response on the original data collection form filed at the site by striking through it (so that it is still legible), writing the correct response, and initialing and dating the corrected item(s). The original response should not be obliterated with white-out, marker, or by scratching through it. The database is similarly updated. After edit queries are resolved, the responses of the database and paper forms must be the same.

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

On occasion, when errors are detected by the Coordinating Center through audits or data summary reports, Coordinating Center staff will have the ability to flag a database response for review by the Clinic Coordinator. A correction to the database and paper form as described above may be required.

### **5.10. QUALITY ASSURANCE RESPONSIBILITIES**

The validity and credibility of the study depends to a large degree on the collection and reporting of high quality, accurate data. Each study 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 trial-related activities. Although the local 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 at the Clinical Center are:

- The person completing each examination and taking responsibility for the examination must be identified by initials and certification number at the end of the section where the data from the examination is recorded.
- Hard-copy documentation of all tests, and procedures should be obtained and kept in patients' study files.
- Any errors or discrepancies discovered at the clinical center are corrected, regardless of the time elapsed since the data were collected, and updated in the database system.
- Systematic data collection or reporting problems are brought to the attention of the responsible individual, the local Principal Investigator and the Coordinating Center for review and resolution.

**EXHIBIT 5-1**

**CATT REQUIRED VISITS & PROCEDURES**

-----FOLLOW-UP WEEK-----

	000	004	008	012	016	020	024	028	032	036	040	044	048	052
<b>History</b>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Refraction</b>	B	B		B			B			B				B*
<b>Visual Acuity</b>	B	B	B	B	B	B	B	B	B	B	B	B	B	B*
<b>OCT</b>	X	X	X	X	V	V	X	V	V	V	V	V	V	X*
<b>Ophthalmologic Exam</b>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Photography</b>	B			F			F							B*
<b>Treatment+</b>	X	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+

-----FOLLOW-UP WEEK-----

	056	060	064	068	072	076	080	084	088	092	096	100	104
<b>History</b>	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Refraction</b>			B			B			B				B
<b>Visual Acuity</b>	B	B	B	B	B	B	B	B	B	B	B	B	B
<b>OCT</b>	V	V	V	V	V	X	V	V	V	V	V	V	X
<b>Ophthalmologic Exam</b>	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Photography</b>						F							B
<b>Treatment</b>	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	X+	

**LEGEND:**

**000:** Denotes 'Baseline visit'

**X:** All patients

**V:** Only patients assigned to the variable dosing schedule.

**B:** Both eyes

**F:** Only for the 300 patients in the fluorescein angiography sub-study (75 patients per treatment arm)

**+:** Treatment for those in the fixed schedule groups. For the variable dosing schedule groups, evaluation for treatment.

**\*** If Week 052 visit is missed, procedure should be done at the next completed study visit that occurs within the week 56, 60 or 64 visit window.

Photography includes both color photography and fluorescein angiography.

## CHAPTER 6

### SAFETY AND ADVERSE EVENTS

#### 6. SAFETY AND ADVERSE EVENTS

##### 6.1. Medical Monitoring in the CATT

Medical monitoring in the Study is the responsibility of the CATT Data & Safety Monitoring Committee (DSMC). A Medical Safety Monitor, who holds an MD, reviews reports of serious adverse events (SAEs) as they occur. On a monthly basis, the Coordinating Center provides the Monitor with the number and type of SAEs at each clinical center, and will provide statistical and analytical expertise to ascertain the presence of site-specific patterns of safety issues.

##### 6.2. Independent Data and Safety Monitoring Board

The Data and Safety Monitoring Committee (DSMC) was appointed by the National Eye Institute and is comprised of ophthalmologists with expertise in age-related macular degeneration and CNV, a specialist in cardiovascular medicine, a physician with expertise in angiogenesis, biostatistician/epidemiologists, and a patient advocate as voting members. The NEI Project Officer serves as an ex officio member. The committee is responsible for the review of performance, safety, and efficacy data. At the first DSMC meeting, the Committee reviewed the study protocol, offered advice to the Study Executive Committee, and approved the study design. Statistical guidelines for early stopping and procedures for recording and reporting adverse events were presented by the Coordinating Center and accepted by the DSMC. The DSMC meets semi-annually.

A Medical Safety Monitor reviews reports of serious adverse events. The Coordinating Center submits periodic reports masked to treatment group to the DSMC and Study Chairman.

##### 6.3. Overview of Adverse Events Definitions and Reporting System

Because the CATT Study is examining the treatment effect of an off-label use of a pharmaceutical agent (Avastin<sup>®</sup>), the study is operating under an IND. Hence this study will comply with the adverse events definitions and reporting requirements for clinical trials established by the Food and Drug Administration (FDA) in 21 CFR 312.

##### 6.4. Definition of Adverse Events

An adverse event (AE) is the development or worsening of any symptom, sign, illness or experience that is temporally associated with a protocol mandated intervention, regardless of causality. These include AEs that emerge during the reporting period that were not previously observed in the patient, complications that occur as a result of protocol-mandated interventions or preexisting medical conditions that are judged by the investigator to have worsened in severity or frequency, or have changed in character during the adverse event reporting period.

## 6.5. Definition of Serious Adverse Events

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs inpatient hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect in a neonate or infant born to a mother exposed to the investigational product
- considered by the investigator to be an important medical event (e.g., events that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the patient, and may require intervention to prevent one of the other serious outcomes noted above.)

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Keep in mind that the definition of a SAE focuses on the “outcome” of the event, and the SAE may involve only one, or possibly more, of the above criteria. All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

### 6.5.1. Severity vs. Serious

The terms “serious” and “severe” are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event (e.g., a mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is *not* the same as “serious”, which is based on patient or event *outcome or action* criteria, usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. When recording AEs and SAEs, severity and seriousness must be independently assessed.

### 6.5.2. Preexisting Conditions

Preexisting conditions should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. If there is a question as to whether a medical development should be reported as an adverse event, the Investigator or Clinic Coordinator must contact the Study Chairman for guidance.

### 6.5.3. Worsening of Symptoms and Signs of Choroidal Neovascularization

Developing symptoms and signs that are consistent with the natural history of choroidal neovascularization secondary to AMD are not considered reportable adverse events. Such developments are, however, recorded on the study data collection forms. For example, moderate loss of visual acuity over time, expansion of the size of the lesion, and increased intraretinal or subretinal fluid are common developments associated with AMD. Such developments are

recorded on study forms by either clinical center staff or staff at the two Reading Centers, but are not reportable adverse events.

Worsening of symptoms and signs of choroidal neovascularization should be recorded as an AE or SAE only if judged by the investigator to have unexpectedly worsened in severity and/or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of choroidal neovascularization, it is important to convey why the development was unexpected. For further guidance see 6.5.6. below.

#### **6.5.4. Abnormal Laboratory Values**

Abnormal laboratory results will generally not be recorded as an AE. A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.
- The abnormality results in study withdrawal.

#### **6.5.5. Hospitalization, Prolonged Hospitalization or Surgery**

Any adverse event that results in a hospitalization should be documented and reported as a SAE. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event when the hospitalization or prolonged hospitalization was for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

#### **6.5.6. Vision Threatening Adverse Events**

An AE is considered to be vision-threatening and is a reportable SAE if it meets one or more of the following criteria:

- It caused a decrease in visual acuity of >30 letters (compared with the last assessment of visual acuity prior to the most recent treatment) lasting >1 hour.
- It caused a decrease in visual acuity to the level of Light Perception or worse lasting > 1 hour
- It required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis).



- In the investigator's opinion, it may require medical intervention to prevent permanent loss of vision.

Note that the development of endophthalmitis is a reportable serious adverse event.

#### **6.5.7. Deaths**

All deaths that occur during the AE reporting period (section 6.6), regardless of attribution to study intervention, must be recorded on a CATT Patient Death Form, entered into the CATT database and immediately reported to the Coordinating Center and local IRB as an SAE. A death certificate must be requested and when obtained, a copy must be sent to the Coordinating Center and the original retained in the patient's CATT file.

#### **6.6. Adverse Event Reporting Period**

The reporting period during which adverse events must be reported is the period from enrollment to the end of the study follow-up. All unresolved adverse events must be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled study visit, the Investigator will instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to prior study treatment. Such events should be reported if the Investigator attributes the event to study treatment. Patients who withdraw early from the study will be contacted by the Clinic Coordinator 30 days after their last visit to ascertain whether any AEs have occurred.

#### **6.7. Collecting Adverse Event Information**

During each study visit, investigators and clinic coordinators will assess the occurrence, status change and resolution of AEs and SAEs by examination and by questioning the patient. Complete reporting information includes the following:

- Specific condition or event and direction or change
- Grade/severity
- Event type
- Dates of onset and (if applicable) resolution
- Outcome
- Whether event necessitated a change in study treatment
- Abnormal laboratory value (SAEs only)
- Attribution to study drug (SAEs only)

Whenever an SAE is associated with a hospital stay, the clinic coordinator must ask the patient to sign a release to obtain the hospital discharge summary. Upon receipt, a copy of the report must be sent to the Coordinating Center and the original filed in the patient's CATT file.

## **6.8. Assessment of Adverse Events**

All events will be coded by the Clinic Coordinator using an on-line version of the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (National Cancer Institute, 2006). The CTCAE version 3.0 provides definitions for a large subset of adverse event terms and a grading (severity) scale for each adverse event. The CTCAEv3.0 and its associated grading criteria are very specific, providing an adverse event term (MedDRA name and number) and grade that precisely describes the event. (Refer to the CATT Oracle Clinical™ Training Manual for instructions in accessing and using the CTCAEv3.0.) If the event is not found in the CTCAEv3.0, the Clinic Coordinator contacts the Coordinating Center for assistance. The Director, Protocol Monitor and Systems Analyst uses MedDRA Browser Version 10 (Northrup Grumman, 2005), which is linked to a database of all MedDRA numbers and terms.

### **6.8.1. Coding Ocular Adverse Events**

When coding an ocular adverse event, the clinic coordinator should first consult the CTCAEv3.0 as described above. If the event is not found, the clinic coordinator should next consult the list of the Common Ocular Adverse Events, which is accessible from the CATT Landing Page ([https://rt4.cceb.med.upenn.edu/crcu\\_html/crcu\\_rdc\\_launch.html](https://rt4.cceb.med.upenn.edu/crcu_html/crcu_rdc_launch.html)). If the event is not on this list, the coordinator then searches the full list of Ocular MedDRA terms, which is also accessible from the CATT Landing Page.

### **6.8.2. Grading the Severity of Adverse Events**

All events must be graded for severity by the Investigator, using a 5 point scale:

- 1 = Mild: Awareness of sign or symptom, but easily tolerated
- 2 = Moderate: Interference with normal daily activities
- 3 = Severe: Inability to perform normal daily activities
- 4 = Life threatening or disabling: Immediate risk of death or disablement
- 5 = Death

### **6.8.3. Attributing the Causality of Serious Adverse Events**

Attribution is the determination of whether a serious adverse event is related to a medical treatment or procedure. To report on attribution, clinicians must evaluate each SAE the patient experiences to determine what might have caused the event or what interventions or conditions might have been associated with the event.

A SAE is related to the investigational agents when 1) the onset is temporally related to the administration of the study drug and the SAE is not explainable by the patient's concomitant conditions or therapies, and/or 2) the SAE follows a pattern of response to the study drug or injection and/or 3) the SAE lessens or resolves when the drug is reduced or discontinued, and (if applicable) 4) reoccurs when drug is reintroduced. A non-related SAE has an etiology other than the study drugs (e.g., preexisting medical condition, underlying disease or concomitant medication) or a SAE whose onset is not plausibly related temporally to the administration of the study drug. When ascertaining whether a SAE is related to the drugs under study, or to the injection procedure, investigators should use the following criteria:

<b>Unrelated:</b>	The SAE is clearly not related to the investigational agents
<b>Unlikely:</b>	The SAE is doubtfully related to the investigational agents
<b>Possible:</b>	The SAE may be related to the investigational agents
<b>Probable:</b>	The SAE is likely related to the investigational agents
<b>Definite:</b>	The SAE is clearly related to the investigational agents
<b>Related to Injection</b>	<b>The SAE is not related to the investigational agent but is related to the injection procedure alone</b>

#### 6.8.3.1. Attribution of Causality by the Medical Safety Monitor

The Medical Safety Monitor will also evaluate all reported SAEs against accumulating knowledge of the study drugs to identify and communicate new safety findings to investigators and to the FDA. In cases when the evaluation of the Medical Monitor regarding causality differs from the Investigator's, the Monitor's assessment will prevail with regard to filing MedWatch reports.

#### 6.9. Recording of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs that are observed during the study are recorded on the CATT Adverse Event Log and in the patient's clinical record. All SAEs are also reported on the CATT Serious Adverse Event Initial Reporting Form (or SAE Follow-up Reporting Form) and submitted to the CATT Coordinating Center. The information recorded on the CATT Adverse Event Log should be based on the signs or symptoms detected during the clinical evaluation of the patient and on information obtained from the patient. The AE Log is included in the on-line CATT database, and with the submission of each log entry the computer performs an automatic data check to ensure that all required reporting elements have been entered into the system.

All serious adverse events are reported on the SAE Initial Reporting Form (or SAE Follow-up Reporting Form) and submitted to a secured fax machine at the CATT Coordinating Center. The Coordinating Center maintains a database of all SAEs and confirms receipt of materials in conjunction with a reminder to the Clinic Coordinator to report the event to the local IRB if the event meets the IRB's reporting requirements. Reports of all SAEs and all accompanying documentation will be electronically sent to the Medical Monitor by the Coordinating Center.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Adverse events that are still ongoing at the end of the study period must be followed up for one month to determine the final outcome. Any AE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

**6.9.1. Diagnosis vs. Symptoms**

If a disease is known at the time an AE is reported, this diagnosis should be recorded on the Adverse Event Log and (if appropriate) on the SAE Reporting Form rather than listing individual symptoms. However, if a cluster of symptoms cannot be identified as a single diagnosis, each individual event should be reported separately. If a diagnosis is subsequently known, it should be reported as follow-up information.

**6.10. Reporting of Serious Adverse Events**

The time frame within which an adverse event must be reported by clinical center staff depends on whether or not it is drug related, expected or unexpected, and degree of severity. The following table summarizes the Requirements for Reporting Serious Adverse Events.

**SUMMARY OF SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS**

<b>Drug Related*</b>	<b>Unexpected<sup>†</sup></b>	<b>Alarming<sup>††</sup></b>		<b>Coordinating Center</b>	<b>IRB</b>
		±	Serious Not Drug-Related Expected ± Alarming	Within 48 hours	Within 5 working days
✓		±	Serious Drug-Related Expected ± Alarming	Within 24 hours	Within 5 working days
✓	✓		Serious Drug-Related Unexpected Not Alarming	Within 24 hours	Within 5 working days
✓	✓	✓	Serious Drug-Related Unexpected Alarming	Immediately	Within 24 hours

\***Drug Related** - There is reasonable possibility the experience may have been caused by the drug/device

<sup>†</sup>**Unanticipated/Unexpected** - An event not noted as expected in the protocol

<sup>††</sup>**Alarming** - (Grade 3 or above)

**NOTE:** Each participating clinical site is required to conform to the reporting rules of their local IRB.

**6.10.1. Reporting Serious Adverse Events to the Coordinating Center**

When CATT Clinical Center staff becomes aware of a serious adverse event, the investigator or clinic coordinator notifies the Coordinating Center via secure fax transmission of the SAE Reporting Form within the time period listed in the table above. Copies of all such correspondence must be maintained in the patient's study folder at the site.

In turn, the Coordinating Center sends an electronic copy of the Serious Adverse Event Report Form and other supporting documentation to the CATT Medical Monitor, CATT Study Chairman and NEI Project Officer within 24 hours of notification by the Clinical Center.

#### **6.10.2. IND Safety Reports**

The CATT Study Chairman holds the IND for the use of Avastin<sup>®</sup> in this trial. He, or at his direction, the Principal Investigator of the Coordinating Center is responsible for notifying the FDA and all participating CATT Investigators of any adverse events that are associated with the study drugs that are both serious and unexpected. Follow-up information to a safety report will be submitted as soon as the relevant information is available.

#### **6.10.3. Written IND Safety Reports**

The CATT Study Chairman or, at his direction, the Principal Investigator of the Coordinating Center notifies the FDA and all participating CATT investigators in a written IND safety report of any event associated with the use of the study drugs that is both serious and unexpected and any finding from laboratory animal testing suggesting a significant risk for humans. Notification occurs as soon as possible, but no later than 15 calendar days after notification of the event. In each written IND safety report, the Chairman will identify all safety reports previously filed with the IND concerning a similar adverse experience and will analyze the significance of the SAE in light of the previous similar reports.

##### **6.10.3.1. Telephone/Faxed Transmission of IND Safety Reports**

The Study Chairman or at his direction, the Principal Investigator of the Coordinating Center, will notify the FDA by telephone or fax of any unexpected fatal or life-threatening event that is associated with the use of the study drugs. Notification will occur as soon as possible, but no later than 7 calendar days after notification of the event.

#### **6.10.4. IRB Notification of SAEs Occurring at Their Center**

The Clinical Center must inform their local IRB of all serious adverse events occurring at the center, in accordance with the IRB's reporting requirements. The Clinic Coordinator indicates on the Serious Adverse Event Report Form the status of this notification or that the SAE does not meet the requirements for IRB notification. Until she/he indicates that the IRB has been notified, or that no notification is required, the Protocol Monitor will contact the Clinic Coordinator on daily basis until she/he submits documentation to indicate that IRB notification has been made. During site visits to the clinical centers, the Protocol Monitor will ensure that documentation exists to confirm that the local IRB was notified of all reportable SAEs that occurred at the site.

#### **6.10.5. IRB Notification of SAEs Occurring at Other Centers**

Upon receipt of an IND Safety Report, each Clinical Center is responsible for copying the IND report and submitting the copy to their local IRB within 10 working days (or shorter if the local IRB requires a shorter reporting period). The original report and dated documentation of IRB submission (via cover letter) must be maintained at the clinical center. During site visits to the clinical centers, the Protocol Monitor will ensure that documentation exists to confirm that the local IRB was notified of all reportable SAEs.

#### **6.10.6. DSMC Notification of Serious Adverse Events by the Coordinating Center**

The Director of the Coordinating Center informs the full DSMC in writing of all serious adverse event reports at semi-annual committee meetings. The Medical Monitor may, at her discretion, instruct the Coordinating Center to notify the full DSMC immediately of a serious adverse event, and may request a meeting or teleconference of the committee prior to its next scheduled meeting.

The following information will be provided to the DSMC by the Coordinating Center:

- Clinical Center
- Patient ID Number
- Description of event (MedRA code)
- Date of onset
- Current status
- Severity of the event
- Whether study treatment was discontinued
- Medical Monitor's assessment of association between SAE and study drugs
- Reason the event is classified as serious

#### **6.11. Annual Reports**

Every year, within 60 days of the anniversary date of the IND, the Study Chairman, or at his direction, the Principal Investigator of the Coordinating Center, will submit to the FDA a report that includes a status report for the study as well as annual summary that includes:

- Tables of the most frequent and serious SAEs by body system
- Summary of all IND Safety Reports
- A list of deceased patients and causes of death
- Drops-out due to adverse events
- (If relevant) a description of new understanding of the study drugs' actions

#### **6.12. Reporting and Analysis of Serious Adverse Events**

Biostatisticians at the Coordinating Center will, on an annual basis, report to the DSMC, the NEI and the FDA their analysis of all cumulative serious adverse events. The analysis will include:

- Number of events
- Frequency of each type of event
- Severity of events
- Attribution of event
- Number of patients who had study drug stopped
- Whether Study drug could be reinstated

- Number of patients requiring medication after stopping Study drug at one and two years
- Number of deaths

### **6.13. Managing Adverse Events**

When a patient enrolled in the study experiences an adverse event, the Investigator at the Clinical Site will manage the patient with the best medical treatment protocol for the condition or, if appropriate, will refer the patient to a specialist or to the patient's personal physician.

### **6.14. Stopping Due to Safety Concerns**

At the first meeting of the Data and Safety Monitoring Committee, the topic of stopping the clinical trial was addressed. Specific complications of treatment are anticipated and specific boundaries, in terms of magnitude of incidence or statistical significance may be adopted. For unanticipated adverse events associated with treatment, the DSMC will consider the severity of the adverse event, the magnitude of the excess incidence, the biological plausibility of a causal relation with the intervention, and the statistical significance of the difference in incidence between treatment groups.

## **CHAPTER 7**

### **REFRACTION AND VISUAL ACUITY TESTING PROTOCOLS**

#### **7. INTRODUCTION**

The refraction and visual acuity testing protocol designed by the Diabetic Retinopathy Clinical Research Network (DRCRnet, 2005) will be used in the Study. The CATT Research Group is indebted to the DRCRnet for sharing their protocol.

ALL refractionists should be proficient in the following optical fundamentals:

- Spherical equivalency
- Plus/minus spheres and cylinders
- Hyperopia, myopia, and astigmatism
- “Push plus” refraction principles.

#### **7.1. REFRACTION CHART**

Use of the refraction chart on the Electronic Visual Acuity Tester (EVA) at a distance of 3 meters is preferred; however, ETDRS chart R (Exhibit 7-1) at 4 meters/1 meter may be used in the rare event that the EVA is not working.

- For the EVA, the refraction chart on the EVA is displayed by tapping on the [Refraction Chart] icon on the Main Menu of the Palm Handheld or tapping the dropdown in upper right corner of screen and selecting ‘Refraction Chart’; select [Refraction Chart] icon
- If the EVA is not functioning and the ETDRS chart R is used for refraction, the refraction protocol described beginning in section 7.4 “Steps in Refraction” should be performed, starting at 4 meters. If the subject is unable to read at least 3 letters on both the 20/200 and 20/160 lines, the subject should be moved to 1 meter, a +0.75 diopter (D) sphere added to the spherical power in the trial frame, and the refraction performed using the appropriate lenses according to the vision level. The refraction obtained at 1 meter must be reported as a 4-meter equivalent by subtracting +0.75 (D) from the spherical power.
- Under no circumstances should the ETDRS charts be used interchangeably with the EVA during the same refraction session.

Check the room lighting level before the refraction. For the EVA, dim incandescent lighting is required; fluorescent lighting should not be used. There should be no glare on the EVA screen and no spotlights. After warming up the EVA for at least 10 minutes, it should be calibrated for size and brightness (see section 7.5.2 for details) For the ETDRS charts, ambient room lighting is approximately 50 foot-candles, with uniform lighting maintained between the subject and the ETDRS charts.

#### **7.2. TRIAL FRAMES/PHOROPTER**

Trial frames are preferred for use in refraction. If trial frames/lenses are not used, a phoropter may be used. If a phoropter is used, the final refraction **MUST** be put in trial frames and the final



spherical refinement performed at 3 meters with the EVA, if the EVA is used, or at 4 meters with the ETDRS chart, if the EVA is not functioning.

If a phoropter is used for a subject whose acuity is worse than 20/80, the +/-0.25 D or +/-0.50 D strength of the phoropter's mounted cross cylinder may not allow the subject to notice any change when checking for cylindrical axis and power. In this case, a separate +/-1.00 D handheld cross cylinder (as in Exhibit 7-2 Protocol Summary at the end of this chapter) held in front of the phoropter instead of the mounted cross cylinder is recommended.

The protocol for the subjective refraction is described in terms of a trial frame, but a similar method can be followed with a phoropter.

The trial frame is placed and adjusted on the subject's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. The left eye is occluded and the starting refraction is placed in the right lens cells, with the cylindrical correction anterior. The steps for the procedure are detailed below.

### **7.3. CONTACT LENS USE**

If the subject wears contact lenses and has spectacle glasses as well, he/she should be instructed to refrain from wearing the contact lenses on the day of each examination. In the event that the subject either has no glasses or has forgotten the instructions and has reported for the examination wearing contact lenses, these should be removed and at least one-half hour should elapse before the refraction is performed. In this latter event, careful attention should be given to the cornea during the slit-lamp examination: any abnormalities should be noted in the subject's clinic record.

### **7.4. STEPS IN REFRACTION**

The following steps must be used during refraction and are explained in more detail below

1. Determine initial starting refraction
2. Refine sphere for the right eye
3. Refine cylinder axis for the right eye
4. Refine cylinder power for the right eye
5. Recheck sphere for the right eye
6. Repeat the process for the left eye

#### **7.4.1. Determine Initial Starting Refraction**

If subject has had a study refraction at a prior visit, use the refraction results from the most recent visit.

If this is the first study refraction for the subject, use one of the following for the starting refraction:

- Retinoscopy
- Autorefractor

- Current spectacles
- Previous refraction (available in subject chart)

In the exceptional case that none of the above is available, then start the refraction with ‘plano’.

The refraction steps below are for visual acuities of 20/20 to 20/80 with the initial starting refraction. For acuities worse than 20/80, refer to the charts for appropriate sphere and cylinder powers to use. Whenever the acuity improves to a better range by improved correction (e.g. from 20/80 – 20/160 range to 20/20 – 20/80 range) smaller sphere and cylinder powers for the better acuity range according to the charts should be used.

## 7.4.2. Refine Sphere

### 7.4.2.1 Increase Plus

	<b>Sphere for Checking</b>	<b>Sphere Incremental Change</b>
<b>20/20-20/80</b>	+0.50	+0.50
<b>&lt;20/80 – 20/160</b>	+1.00	+1.00
<b>20/200 – 20/320</b>	+2.00	+1.00
<b>&lt;20/320</b>	+2.00	+1.00

The right eye is tested first and then the left eye. The starting refraction is placed in the trial frame; the left eye is occluded with an occluder lens and tissue or eye patch and the refractionist determines the lowest line that the subject can read.

With the subject focused on the smallest letters that he/she can read, a +0.50 D sphere is held in front of the trial frame over the right eye and the subject is asked if the lens makes the vision clearer, blurrier, or keeps the vision exactly the same.

- NOTE: “Clearer, Blurrier, or No Change” preferred, but “Better, Worse, or No Change” can be used. If vision is clearer or there is no change, the sphere in the trial frame is replaced with a sphere that is 0.50 D more plus or less minus.
- The +0.50 D sphere is again held in front of the trial frame over the right eye and the subject is asked again if the lens makes the vision clearer, blurrier, or keeps the vision exactly the same.
  - If vision is again clearer or there is no change, the sphere in the trial frame is replaced with a sphere that is 0.50 D more plus or less minus.
- This process of increasing the plus sphere or decreasing the minus sphere in the right eye is repeated until the +0.50 D sphere makes the vision blurrier.
- When the +0.50 D sphere makes the vision blurrier, no additional change in the sphere is made at this time.

By this process the highest plus or least minus sphere for best vision is determined.

#### 7.4.2.2. Increase Minus

	<b>Sphere for Checking</b>	<b>Sphere Incremental Change</b>
<b>20/20-20/80</b>	-0.50 (or -0.37)	-0.25
<b>&lt;20/80 – 20/160</b>	-1.00	-0.50
<b>20/200 – 20/320</b>	-2.00	-1.00
<b>&lt;20/320</b>	-2.00	-1.00

After determining the highest plus or least minus sphere, the subject is asked to read the smallest line possible (the reading should be at least as good as the initial reading).

The -0.50 (or -0.37) D sphere is held in front of the trial frame before the right eye and the subject is asked if the vision is improved so he/she can actually read more letters.

- If vision is not improved, the +0.50 D sphere is held in front of the trial frame before the right eye once again to see if the subject will accept more plus.
- If the subject reports that the -0.50 (or -0.37) D lens improves vision, the subject is requested to read the smallest line possible while the -0.50 (or -0.37) D lens is held in front of the trial frame.
  - If there is an actual improvement in acuity and the examiner is convinced that the subject is able to read at least one additional letter, then the sphere in the trial frame is replaced by a sphere that is 0.25 D less plus or more minus.

Minus spherical power is added in -0.25 D increments in this fashion as long as the subject continues to read at least one additional letter.

- If the subject is unable to read any more letters, the sphere is not changed, even if the subject reports that the vision with the extra minus is better (or sharper and darker or more distinct).

The final check in the initial sphere evaluation is the presentation of a +0.50 D sphere to determine if any more plus sphere will be accepted initially.

**Example:** Assume that following the check with plus sphere, the sphere in the trial frame is -0.50. The subject is asked to read the lowest line possible with this correction and reads the 20/20 line perfectly and no letters on the 20/16 line. Then -0.50 (or -0.37) D is held in front of the trial frame and the subject is asked if the lens makes the vision clearer or blurrier. If the subject reports that the vision is clearer, he is again asked to read the chart. If more letters are read (e.g., 20/20<sup>+2</sup>), then the sphere in the trial frame is changed to -0.75.

The process is repeated with a -0.50 (or -0.37) D added over -0.75. If again the subject reports that vision is improved, but he/she cannot read any additional letters, the sphere should remain at -0.75 and a final sphere check with a +0.50 D lens done.

### 7.4.3. Refine Cylinder Axis

For purposes of this discussion, only plus cylinder techniques are presented. Minus cylinders may be used instead of plus cylinders to determine the axis and power of the cylinder. If minus cylinders are used, the procedure described must be revised to reflect this change in sign.

If the starting refraction contains a cylinder correction, changes in cylindrical axis are tested by holding a 0.50 D cross cylinder in front of the trial frame (or the appropriate cross cylinder based on level of acuity), 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 (in most cases, the handle of the Jackson Cross Cylinder lens should be aligned directly over the axis of the cylinder lens in the trial frame).

Instruct the subject to focus on an “O” or “C” one-two lines above the smallest line of letters that he can read.

Explain to the subject: *I am going to show you two views of this “C” and neither view may be clearer than the view you have right now. I would like to know which of the two views is the clearer of the two, or are both views pretty much about the same or equally blurry. Ask: Is the “C” clearer on view 1 [flip the lens] or view 2, or are both views about the same or equally blurred?*

- Since neither position may produce a clear image, the subject is encouraged to select the position of least blur.

If the subject cannot choose between the two positions of the cross cylinder at the beginning of this test, the axis of the cylinder is moved 5-15 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 subject does prefer one position of the cross cylinder to the other, the axis of the cylinder is moved 5-15 degrees toward the positive axis of the cross cylinder when in the position the subject said was better.

When the power of the cylinder is low and/or the subject’s discrimination is poor, larger shifts will produce more clear-cut responses.

The cross cylinder is tried again with the positive axis 45 degrees to one side of the new cylinder axis and then with the positive axis 45 degrees to the opposite side of the new cylinder axis; the subject is asked which position he/she prefers.

- If the subject prefers one position to the other, 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 subject cannot decide that one position of the cross cylinder is clearer than the other by reporting that both views are about the same or equally blurry.

#### 7.4.4. Refine Cylinder Power

Change in cylinder power is now tested by adding the 0.25 D cross cylinder (or appropriate cross cylinder based on level of acuity), first with the positive axis and then with the negative axis coincident with the cylinder axis.

Again, instruct the subject to focus on an “O” or “C” one-two lines above the smallest line of letters that he/she can read or on the smallest line of letters he can read. Explain to the subject: *Once again I am going to show you two views of this “C” and neither view may be clearer than the view you have right now. I would like to know which of the two views is the clearer of the two, or are both views pretty much about the same or equally blurry. Ask: Is the “C” clearer on view 1 [flip the lens] or view 2, or are both views about the same or equally blurred?*

- If the subject prefers the positive axis coincident with cylinder axis, the power of the correcting plus cylinder is increased by an additional plus 0.25 D.
- If the subject prefers the negative axis coincident with the cylinder, the power of the cylinder is reduced by 0.25 D.

The process is repeated until the subject cannot choose one of the cross cylinder positions as better than the other (i.e., until both positions are about the same or equally blurred).

Whenever the cylinder is changed by 0.50 D, 0.25 D of sphere of opposite sign is added as well (the changing of the sphere occurs during the procedure as soon as the cylinder has been changed by 0.50 D rather than making the adjustment following the completion of the refinement).

##### 7.4.4.1 Checking Cylinder When Beginning Refraction is a Sphere

If the beginning refraction is a sphere and does not contain a cylinder, the presence of astigmatism can be tested by one of two methods:

1) Instruct the subject to focus on a letter “C” or “O” one-two lines above the smallest line of letters that he can read. Arbitrarily place a plus cylinder (for plus cylinder refraction) appropriate for the current acuity at 90 degrees, 180 degrees, 45 degrees, and 135 degrees in the trial frame and ask the subject if the lens makes the “C” or “O” clearer. If the subject reports that the cylinder makes the “C” or “O” clearer in any of these locations, continue the refraction by modifying the cylinder axis and power as described above.

2) Arbitrarily insert a +0.25 cylinder (or power appropriate for the current acuity) into the trial frame at 90 degrees, 180 degrees, 45 degrees, and 135 degrees. Using a Jackson Cross Cylinder appropriate for the current acuity, check the cylinder power at 90 degrees, 180 degrees, 45 degrees, and 135 degrees. If the subject accepts the cylinder in any of these locations, insert a cylinder of that strength at the accepted axis in the trial frame and continue the refraction by modifying the cylinder axis and power as described above.

#### 7.4.5. Refraction Recheck/Final Sphere Refinement

The power of the sphere is rechecked according to the sphere refinement protocol above by using +0.37 D and -0.37 D spheres and changing the spherical power by 0.25 D increments of the appropriate sign until the subject reports that the +0.37 lens blurs the vision and the -0.37 does not improve vision. If the sphere is changed at this point by 0.50 D or more, the cylinder axis and power should be rechecked. This process is repeated until no further significant lens changes are made. In refractions using the phoropter and the EVA, a final check of the sphere as described above **must** be repeated using the EVA (at a distance of 3 meters) and trial frames.

*The entire process is then repeated for the left eye .*

#### 7.4.6. Refraction for Subjects with Poor Visual Acuity

For subjects with acuity worse than 20/100, the strong preference is to use the EVA at 3 meters since letters can be projected as large as 20/800. The EVA chart is a three-meter chart and should not be moved closer to the subject.

When the ETDRS chart R is used, if the subject is unable to read at least 3 letters on both the 20/200 and 20/160 lines, the subject should be moved to 1 meter, a +0.75 diopter (D) sphere added to the spherical power in the trial frame, and the refraction performed using the appropriate lenses according to the vision level. The refraction obtained at 1 meter must be reported as a 4-meter equivalent by subtracting +0.75 (D) from the spherical power.

If the subjective refraction cannot be performed because the subject's visual acuity is too poor, then the subject's most recent distance subjective refraction obtained at a previous visit should be considered as the refraction.

**Example 1:** ETDRS chart R is used for refraction which could not be performed at 4 meters in the study eye because the subject could not see any letters on the refraction chart at that distance. When the subject was moved up to 1 meter, the following was obtained: + 2.00 + 1.00 x 180 degrees

In order to make this finding appropriate for visual acuity testing at 4 meters, a +0.75 D sphere must be subtracted from the above correction, resulting in + 1.25 + 1.00 x 180 degrees for the final refraction.

**Example 2 :** ETDRS chart R is used for refraction which could not be performed at 4 meters in the right eye because the subject could not see any letters on the refraction chart at that distance. When the subject was moved up to 1 meter, the following was obtained: - 1.00 + 1.00 x 180 degrees. In order to make this finding appropriate for visual acuity testing at 4 meters, a +0.75 D sphere must be subtracted from the above correction, resulting in -1.75 +1.00 x180 degrees for the final refraction.

## 7.5. VISUAL ACUITY TESTING

It is essential to have standardized visual acuity measurements for each examination at each of the participating clinics to minimize the effects of acuity examiner and subject bias. Visual acuity testing is performed with the Electronic Visual Acuity Tester (EVA) using a protocol called the Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol. This protocol has been developed to provide a visual acuity score that is comparable to that using the manual testing protocol used in the Early Treatment of Diabetic Retinopathy Study (ETDRS). The ETDRS chart testing is used as a back-up in case the EVA is not functioning.

Visual acuity measurements for each eye are obtained by a CATT-certified visual acuity examiner before the subject's pupils have been dilated.

### 7.5.1. Electronic Visual Acuity Tester

#### 7.5.1.1 EVA System Description

The EVA (Figure 1) utilizes a programmed Palm handheld device (or tablet PC) that communicates with a personal computer running a Linux (or Windows XP) operating system.

Stimuli are high-contrast, black-and-white letters with luminance of 85 to 105 candels/meter<sup>2</sup> and contrast of 98%. The system can present single letters or lines of letters. Single letter testing is used in the Electronic ETDRS program whereas lines of letters can be used for refraction. Single letters are framed with crowding bars spaced a letter width around the letter. For lines of letters, five letters are displayed for sizes smaller than 20/160; a decreasing number of letters is displayed as letter size increases. With a high-resolution (1600x1200) 17-inch monitor, the system is capable of displaying letters from 20/800 (1.6 logMAR) to 20/12 (-0.2 logMAR) at a test distance of 3 meters. Letter size is a close, but not exact, approximation of the logMAR progression of the ETDRS charts (within about 2% of the letter size at each logMAR level).

The Palm™ handheld device (Figure 2), communicating with the EVA through a connected cable or wirelessly with Bluetooth, provides instructions for the technician, allows entry of identification data, displays the letter that is being shown on the monitor, records the responses, and sends instructions to the EVA with regard to the sequence of letter presentations. The size of each letter presentation is determined by a computer program based on the subject's responses.

**Figure 1: Electronic Visual Acuity Tester (EVA)**



**Figure 2: Palm Handheld**



## 7.5.2. System Calibration

Two system calibrations are performed at regular intervals: (1) size calibration to confirm letters are accurately displayed and (2) luminance calibration to confirm the monitor screen is sufficiently bright for testing.

### 7.5.1.1 Size Calibration

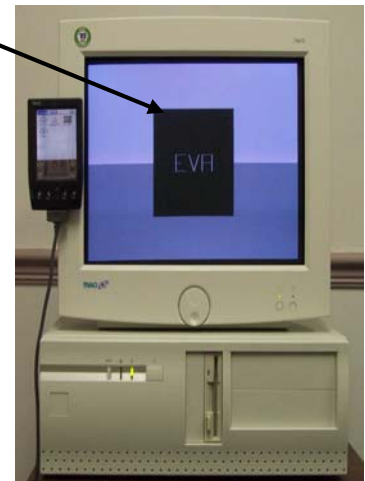
Size calibration must be performed at each study visit. For non-study use, size calibration is recommended at least quarterly.

#### **Size Calibration Instructions:**

1. Display the EVA calibration square (this is the initial screen when the system starts up). Length of each side of the black square should be **114 mm**
2. Repeat the following steps on the top and left side of square:
  - a) Place EVA ruler (or similar ruler with millimeter scale) against side of black square. Check whether length of the side is **114 mm**.

**IMPORTANT:** When viewing, use only one eye and move your head as necessary such that your eye is directly on line with side.

- b) If needed, adjust side to 114 mm by changing horizontal and/or vertical setting on the monitor. Refer to the EVA Users Manual for instructions specific to your monitor.



### 7.5.2.1 Luminance Calibration

Luminance calibration must be performed at each study visit.

#### **Luminance Calibration Instructions:**

1. Allow monitor to warm up for at least 10 minutes.
2. Display the EVA calibration square (this is the initial screen when the system starts up).
3. For luminance calibration instructions specific to your EVA Model, monitor, and light meter, refer to the EVA Users Manual .



### **7.5.3. Adjusting the Monitor Settings**

If the EVA monitor needs size or luminance adjustment, refer to your EVA Users Manual for instructions specific to your EVA model, monitor, and light meter.

### **7.5.4. E-ETDRS Testing Protocol**

The EVA runs a visual acuity testing program called E-ETDRS (which stands for Electronic Early Treatment of Diabetic Retinopathy). The program has been developed to provide a visual acuity letter score that is comparable to the ETDRS chart testing score.

As part of the development of the E-ETDRS protocol, a study was conducted in which high validity and test-retest reliability were demonstrated (Moke et al., 2001).

#### **7.5.4.1 Overview of E-ETDRS Visual Acuity Testing Protocol**

In brief, the E-ETDRS Visual Acuity Testing Protocol consists of an initial screening phase to obtain an approximation of the visual acuity threshold and then a testing phase to obtain the visual acuity score.

The protocol is summarized below (Figure 3). The complete algorithm is depicted in Figure 4 that follows.

**Figure 3**  
**Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol Overview**

The E-ETDRS testing protocol:

- Screening phase: With single letter presentations, determines smallest logMAR level at which a letter is correctly identified.
- Testing phase: Starts testing letters by intermixing letter sizes of screening phase score and one level smaller.
- Test progress: If a letter is missed at a level, one level larger is added to the testing mix; if a letter is correct at a level, one level smaller is added to the testing mix.
- Acuity determination: Tests 5 letters at each level until smallest level with 5/5 correct and the smallest level with 0/5 correct are determined.

*IN THE FOLLOWING EXAMPLE, C = CORRECT AND M = MISSED*

**Example:**

Screening: 20/400c, 20/200c, 20/100c, 20/50c, 20/25m, 20/40m                      Score = 20/50

Test progress

1. Start by intermixing 20/50 and 20/40 letters: 20/50c, 20/40m, 20/50c, 20/40m, 20/50m
2. Because a 20/50 letter was missed, add 20/63 to the letter mix (so now will have letters of 20/40, 20/50, and 20/63 intermixed): 20/63c, 20/50c, 20/40c
3. Because 20/40 was correct, add 20/32 to the letter mix (mix is now 20/32, 20/40, 20/50, and 20/63): 20/32m, 20/63c, 20/63c, 20/50m
4. Five letters at 20/50 have been tested, so it drops out of the mix (mix is now 20/32, 20/40, and 20/63): 20/63c, 20/40c, 20/32m, 20/40m
5. Five letters at 20/40 have been tested, so it drops out of the mix (mix is now 20/32 and 20/63): 20/32m, 20/32m, 20/63c
6. Five letters at 20/63 have been tested, so it drops out of the mix (mix is now 20/32 only): 20/32m
7. Five letters at 20/32 have been tested; there are no letters left in the mix so test is over

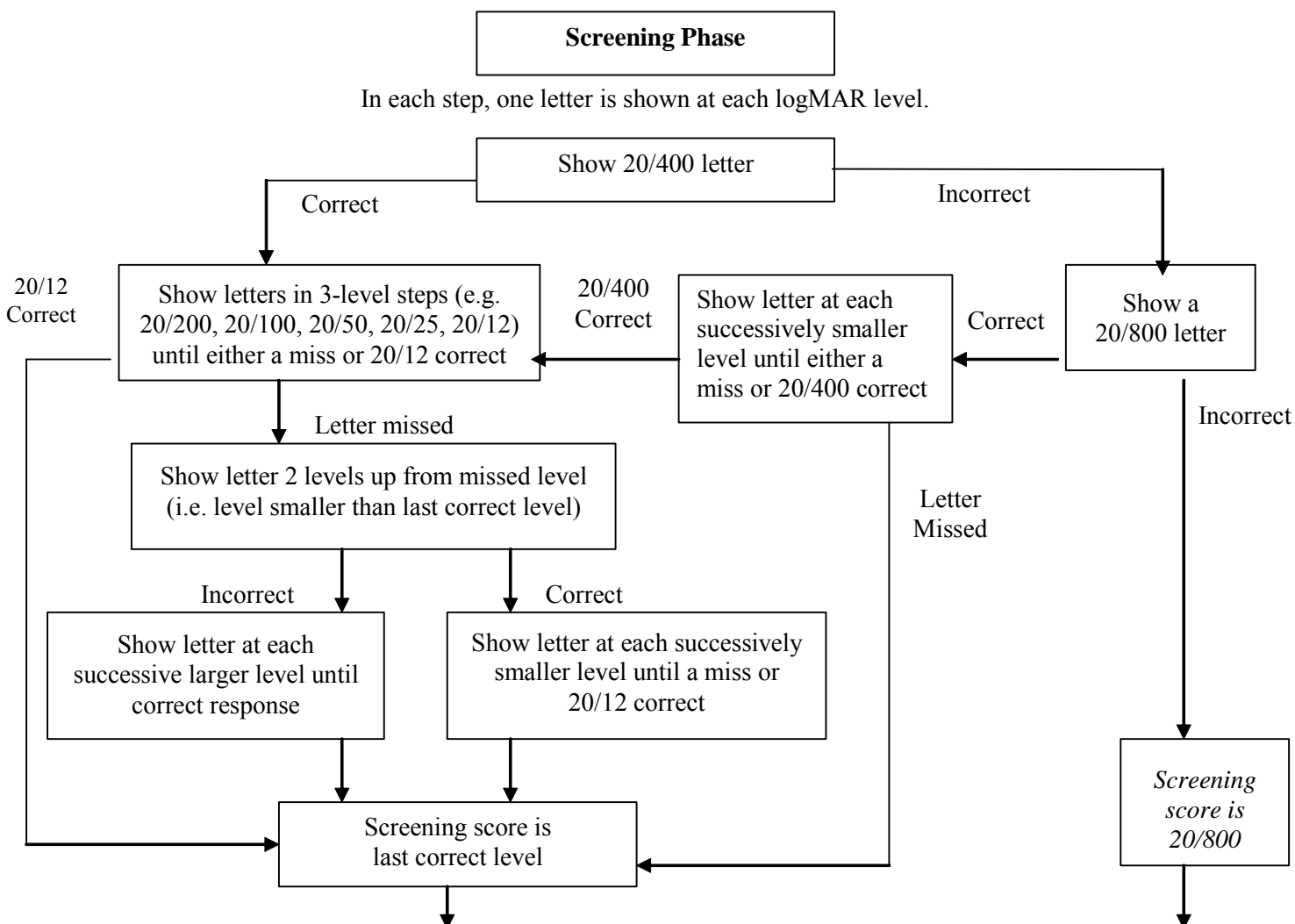
Test summary

20/63    5/5 correct  
20/50    3/5 correct  
20/40    2/5 correct  
20/32    0/5 correct

Letter Score:                      10 (number of letters correctly identified)  
   + 55 (5 times the number of lines above (larger than) 20/63 and through 20/800)  
   = 65

Snellen Notation (smallest line with at least 3 of 5 letters correct): 20/50

**Figure 4**  
**Electronic ETDRS (E-ETDRS) Visual Acuity Testing Protocol Algorithm**



**Threshold Phase**

1. To start, letter pool consists of letters from 2 levels\*: level of screening phase score and one level smaller.
2. Each letter presentation is randomly selected from active pool of letters with the stipulation that every third letter must be from the largest level in active letter pool.
3. A level remains in active pool until 5 letters are tested at the level.
4. A new level is added to active letter pool when:
  - a. A letter from largest level in the pool is missed: one level larger is added to letter pool†
  - b. A letter from smallest level in the pool is correct: one level smaller is added to letter pool‡
5. Testing continues until an upper logMAR level with 5 of 5 letters correct and a lower logMAR level with 0 of 5 letters correct are determined and 5 letters are tested on all levels in between upper and lower logMAR levels.§
6. Visual acuity score is the number of letters correctly identified during threshold testing, plus 5 letters for each logMAR line above the upper logMAR level through 20/800.

The screening phase uses the letters V, R, K and D. The threshold phase uses the same 5 letters from the Sloan letter set that appear on the original ETDRS charts for right and left eyes.

\*Unless screening score was 20/12, in which case letter pool consists of only 20/12 level letters.

†Unless 20/800 letter is missed.

‡Unless 20/12 is correct.

§If 20/12 becomes part of the active letter pool, it will be the lower logMAR level.

## Testing Procedures Using the EVA

### **Before each subject study visit:**

- Calibrate monitor for letter size
- Check monitor luminance
- Check room lighting level (dim incandescent lighting is recommended; fluorescent lighting should not be used; no glare on screen; no spotlights)

### **Before Every Test**

- Verify testing distance from EVA to center of exam chair is 3 meters (118 inches)
- Turn on Palm and remove stylus

### **CATT Subject Testing (must be used for study subjects)**

- Turn on Palm and remove stylus
- On main menu, tap E-ETDRS icon, then choose CATT from studies list  
OR  
Tap dropdown in upper right corner of screen, tap EVA Applications; select E-ETDRS icon; then choose CATT from studies list
- Follow instructions on Palm

### **Shut Down System**

- Turn off the PC tester by selecting [Shutdown] icon on main menu  
OR  
Briefly press and release the power button on the EVA tower.

## **7.5.5. Visual Acuity Testing Procedures**

**7.4.5.1** Trial frames are to be used for refractive correction. In addition to the occluder in the trial frame, for testing the right eye, left eye is occluded with an eye patch or pad placed beneath the trial frames and vice versa.

- If refraction is required at a visit, then the correction determined by the protocol refraction will be used for the visual acuity testing. If refraction is not required at a visit, then the correction determined in the most recent refraction will be used.
- If during a visit when refraction is not required the subject appears to have experienced a loss of vision that cannot be explained by clinical findings on OCT and/or fluorescein angiography and the subject has already had their eye dilated, the subject may be asked to return to the clinic within a week for refraction and visual acuity testing before a decision on treatment is made.

### **7.5.5.2 Testing both eyes at Study Visits**

Both eyes are tested at CATT study visits. The right eye is always tested first, then the left eye.

## **7.6. SAFEGUARDS TO AVOID BIAS**

Masking of the visual acuity examiner is an important feature in avoiding bias in measuring what is the CATT primary outcome. In addition to masking, the automated nature of the computerized EVA testing minimizes the potential for induction of bias on the part of the examiner.

Technician instructions to the subject are to be minimal.

- a. The subject should be told that there are only letters and no numbers and that each letter is “bracketed” by lines on all four sides.
- b. For subjects with poor central vision, it may be suggested that the subject fixate eccentrically or turn or move his/her head in any manner if this improves visual acuity. If the subject employs these maneuvers, care must be taken to ensure that the fellow eye remains covered.
- c. When the subject cannot read a letter, he/she is told to guess. If the subject states that a letter is one of two letters, then he/she is asked to choose only one letter and, if necessary, to guess.
- d. When the subject gives one response but then gives a second response before the first response has been finalized (i.e., before the technician has verified the response as correct or incorrect and before the letter presentation on the EVA screen changes), the subject should be asked if that is his/her final answer; if the subject equivocates, ask the subject to choose one letter. Once the technician has verified the response and the letter presentation has changed on the EVA, no changes can be made in the subject’s response.
- e. If the subject provides a number or any other response other than one of the 26 letters of the alphabet, the subject should be told again that there are only letters on the chart and to respond with a letter.

## **7.7. POOR VISION TESTING (TESTING LIGHT PERCEPTION)**

If the subject cannot identify any letters on visual acuity testing of an eye (i.e., letter score = 0), the eye is tested for light perception with the indirect ophthalmoscope as the light source. The testing procedure can be performed according to the investigator’s usual routine. The following procedure is suggested:

- Room lighting should remain at the level of normal visual acuity testing. The subject should close the opposite eye and occlude it by making a tight seal with the palm around the orbit and the bridge of the nose. The indirect ophthalmoscope light should be in focus at three feet, and the rheostat set at six volts. From a distance of three feet the beam should be directed in and out of the eye at least four times; the subject should be asked to respond when he/she sees the light. If the examiner is convinced that the subject perceives the light, vision should be recorded as light perception, otherwise as no light perception.

## **7.8. STANDARD ETDRS VISUAL ACUITY PROTOCOL**

The Standard ETDRS Visual Acuity Protocol should only be used as a back-up in the event the Electronic Visual Acuity Tester (EVA) is not functioning.

### **7.8.1. Visual Acuity Chart: Modified Bailey-Lovie**

The ETDRS visual acuity charts 1 and 2 will be employed for standardized measurement of visual acuity. Acuity testing of all subjects, regardless of visual acuity, begins at four meters. Two ETDRS Visual Acuity Charts are used for the measurement of visual acuity, each with a different letter sequence. The right eye will always be tested with Chart 1 and the left eye with Chart 2.

### **7.8.2. Illumination of Visual Acuity Charts and Room**

Each clinic must have/use an ETDRS light box for the ETDRS visual acuity charts during any CATT protocol acuity testing when the EVA is not functioning. The light box should be hung at eye level on the wall or placed on a stand (that can be purchased from the Lighthouse for the Blind in New York). Room lighting should be at office levels and should be uniform between the subject and the light box. The distance from the center of the exam chair to the Visual Acuity Chart should be 4.0 meters.

### **7.8.3. Best-Corrected Visual Acuity Measurements**

The right eye is tested first and then the left eye. The subject is seated such that the distance from the center of the exam chair to the ETDRS Visual Acuity Chart should be 4.0 meters. This testing distance is always used first even if the subject could not be refracted at four meters. In addition to the occluder in the trial frame, the left eye is occluded with an eye patch or pad placed beneath the trial frames. With the lens correction obtained by subjective refraction in the trial frame, the subject is asked to read ETDRS Visual Acuity Chart 1 from the top with the right eye. It is emphasized to the subject that each answer will be scored so that adequate time should be allowed for each letter in order to achieve the best identification. The subject is instructed that all of the figures to be read are letters and that there are no numbers.

The examiner records each letter identified correctly by the subject as he/she reads the chart by circling the corresponding letter on the CATT ETDRS Chart worksheet data collection form. Letters read incorrectly, or for which no guesses are made, are not marked on this form. Each letter read correctly is scored as one point. The score for each line (including zero if no letters were read correctly on that line) and the total score for the eye must be recorded on the form after the testing has been completed.

If the number of letters read correctly at four meters is less than twenty, the test should be repeated at one meter and both the four-meter and one-meter totals should be recorded on the CATT ETDRS Chart worksheet data collection form. Both eyes should be tested at four meters before the subject is moved up to the one-meter test distance. Prior to actual testing at one-meter, + 0.75 sphere should be added to the correction already in the trial frame to compensate for the new distance. The subject must sit for testing at the one-meter distance.

The same procedure for obtaining visual acuity for the right eye is used for the left eye, except that ETDRS Visual Acuity Chart 2 is used.

#### **7.8.4. Poor Vision Testing**

Follow the procedures described in section 7.7.

#### **7.8.5. Calculating the Visual Acuity Score**

After each measurement of visual acuity, the visual acuity score for the visit is calculated. The visual acuity score is defined as follows:

- If twenty or more letters are read correctly at the four-meter test distance, the visual acuity score is equal to the number of letters (N) read correctly at four meters +30. If one or more but less than twenty letters are read correctly at four-meter distance, the visual acuity score is equal to the number of letters read correctly at four meters plus the number of letters read correctly at one meter in the first six lines.
- If no letters are read correctly at either the four-meter distance or the one-meter distance, the visual acuity score is 0.

EXHIBIT 7-1  
ETDRS CHART R

20/200	H	V	Z	D	S
20/160	N	C	V	K	D
20/125	C	Z	S	H	N
20/100	O	N	V	S	R
20/80	K	D	N	R	O
20/63	Z	K	C	S	V
20/50	D	V	O	H	C
20/40	O	H	V	C	K
20/32	H	Z	C	K	O
20/25	N	C	K	H	D
20/20	Z	H	C	S	R
20/16	S	Z	R	D	N
20/12.5	H	C	D	R	O
20/10	R	D	O	S	N



## EXHIBIT 7-2

### CATT REFRACTION PROTOCOL SUMMARY

#### FLOW CHART OF CATT REFRACTION PROTOCOL

- 1. SPHERE**
- a. Plus** (lowest line) → → → Clearer → → → Increase plus.  
 No Change → → → Increase plus.  
 Blurrier → → → STOP
- b. Minus** (lowest line) → → → Clearer → → → Increase minus if additional letter(s) read.  
 No Change → → → STOP  
 Blurrier → → → STOP
- c. Plus** (lowest line) → → → Clearer → → → Increase plus.  
 No Change → → → Increase plus.  
 Blurrier → → → STOP
- 2. CYLINDER**
- a. Axis** (C or O above smallest line) → → → Clearer at 1 or 2 → → → Move axis toward preferred plus axis until position 1 and 2 are equal.
- 3. CYLINDER**
- a. Power** (C or O on smallest line) → → → Clearer at 1 or 2 → → → Increase or decrease plus power until neither position 1 or 2 is better. If power changes by  $\geq 0.50$  adjust sphere.
- (Not present)** → → → → → JCC at 90/180; JCC at 45/135 → → → Place 0.25D cylinder at preferred axis. Then, check cylinder axis and power as above.
- 4. REFINE SPHERE** Refine with +/- spheres as in step #1 until no improvement in vision.

**NOTE: “Clearer, Blurrier, No change” preferred; “Better, Worse, No change” may also be used**

Vision with Best Correction	Sphere		Cylinder			Sphere Refinement	
	Power (1)	Increment (1)	Axis (2)	Power (3)	Increment (3)	Power (4)	Increment (4)
20/20 – 20/80	a. +.50	+.50	a..50	a..25	+.25	a.+37	+.25
	b. -.50/-.37	-.25	JCC	JCC	-.25	b. -.37	-.25
	c. +.50	+.50				c.+37	+.25
<20/80 – 20/160	a. +1.00	+1.00	a.1.00	a.1.00	+1.00	a.+50	+50
	b. -1.00	-0.50	JCC	JCC	-1.00	b. -.50	-.50
	c. +1.00	+1.00				c.+50	+50
20/200 – 20/320	a. +2.00	+1.00	a.1.00	a.1.00	+1.00	a.+1.00	+1.00
	b. -2.00	-1.00	JCC	JCC	-1.00	b.-1.00	-1.00
	c. +2.00	+1.00				c.+1.00	+1.00
<20/320	a. +2.00	+1.00	No cylinder test			No refinement	
	b. -2.00	-1.00					
	c. +2.00	+1.00					

## CHAPTER 8

### PROCEDURES FOR FUNDUS PHOTOGRAPHY

#### 8. INTRODUCTION

Good quality stereoscopic fundus photographs are required to describe pathology present and to determine whether an eye meets the eligibility criteria for CATT. A detailed photographic protocol will ensure consistently high quality photographs as well as standardization of camera equipment, image acquisition, and film processing.

The digital imaging systems at the clinical centers must be certified by the CATT Fundus Photograph Reading Center (CATT FPRC) before patients can be enrolled. CATT requires that both color photographs and fluorescein angiograms be digital images. However, a clinical center can be certified to submit film images if the requirement for certification can not be met. It is not acceptable for a clinical center to obtain images on film and then digitize them with the use of a scanner. Digital images must be obtained with an acceptable CATT-certified digital imaging system.

Photographers must be CATT certified before photographing Study patients. (See Chapter 14, Clinical Center Staff Responsibilities and Certification Requirements) Clinical centers are strongly urged to have at least 2 photographers certified.

The CATT photography protocol incorporates procedures already established for multiple clinical trials by the University of Wisconsin Fundus Photograph Reading Center (UW-FPRC).

*Modified 3-Standard Field Color Fundus Photography and Fluorescein Angiography Procedures. University of Wisconsin Fundus Photograph Reading Center (UW-FPRC). October 16, 2000.*

<http://eyephoto.ophth.wisc.edu/Photographers.html>

*Digital Fluorescein Angiography. Supplement to the Modified 3-Standard Field Color Fundus Photography and Fluorescein Angiography Procedures. Digital FA Module ver 4.1 (May 2004).*

<http://eyephoto.ophth.wisc.edu/Photographers.html>

Although not yet accepted as a standard, DICOM (Digital Imaging and Communications in Medicine) format will be supported by the Reading Center if a digital imaging system does not support exportation of files in BMP or TIFF file formats.

All color photographs and fluorescein angiograms are submitted to the CATT FPRC for evaluation (See Chapter 17, Fundus Photography Reading Center).

## 8.1. Required Photography

The required color photographs and fluorescein angiograms are the same if acquired digitally or on film. Stereo color photographs of fields 1M (modified field 1) and 2 of **both eyes** and a stereo fluorescein angiogram are required at weeks 000 (baseline), 052 and 104. For a substudy of 300 patients at selected centers, color photographs and a stereo fluorescein angiogram are also required at weeks 012, 024, and 076 (See Exhibit 8-1 Required Fundus Photography).

Initial visit photographs and fluorescein angiograms must be obtained within 7 days prior to randomization.

When follow-up visit photographs are required they should be obtained the day of the visit. If a treatment injection is to be administered, photographs must be taken before the injection. If required photographs are not taken before the injection, photographs are not to be taken after the injection. In extraordinary cases (e.g., camera malfunction, sudden patient illness), when no injection is given in connection with the visit and photographs were required, photographs may be taken within 7 days of the visual acuity measurement for the visit.

## 8.2. DIGITAL IMAGING SYSTEM CERTIFICATION

Prior to photographing study patients, each digital imaging system must be certified by the CATT FPRC. The Reading Center may require modifications to the system before granting certification. Any changes in the digital system that occur after the system is certified (including software and hardware changes) must be reported to the CATT FPRC immediately after they are made and may require system re-certification.

The following steps are required (All forms are available on the CATT Remote Data Capture website):

- Submit a CATT Digital Imaging System Information Questionnaire to the CATT FPRC
- Install the CATT Submission Application provided by the CATT FPRC on the local hard drive (Follow the instructions provided with installation CD.)
- Using the digital system to be certified, identify digital angiograms and digital color stereo pairs of fields 1M and 2 of two patients (see Section 8.4.)
- All images should be uncompressed and the patient's name removed from all images and files to be submitted
- Print the CATT Image Data Submission Sheet as prompted within the Submission Application
- Copy the image files to a CD-R using the CATT Submission Application
- Fill in the "Center #, Site #, Date of the images, and Submitted by" on the CD label provided by the CATT FPRC. Check the System box.

- Submit the CD to the Reading Center along with a CATT Digital Imaging System Certification Form and the CATT Image Data Submission Sheet. A separate CD and form are created for each system.
- The CATT FPRC may test the “dial-in” access for later troubleshooting
- Once certification is complete, a separate certification number will be issued for each system for identification purposes

### **8.2.1. Digital Imaging System Requirements**

Topcon IMAGENet® System, Ophthalmic Imaging System (OIS) WinStation®, MRP or Zeiss Visupac digital systems are acceptable for CATT. An alternate ophthalmic digital imaging system may be approved if all the requirements for acquisition, archiving, magnification, image quality, and image accessibility by the CATT FPRC can be met. Systems must use a Microsoft Windows XP or higher operating system (no DOS or Macintosh systems) and must have CD writing capability. Digital images should be approximately 1 MB (uncompressed) or larger.

It is preferred that the digital system contains software and hardware that allows remote access and operation. The Reading Center or their representative may inspect the digital camera system to assure that all capture settings are correct for accurate image analysis. This inspection may be performed via “dial-in” access or as part of a site visit. Inspection software may be used to verify and record system settings.

In order to account for possible differences in image quality and magnification even among similar systems, each individual digital imaging system and accompanying camera requires certification. If the digital imaging system cannot meet the certification requirements, the clinical center can apply for certification as a film-based angiography site with an acceptable camera. Scanning Laser Ophthalmoscope (SLO) based cameras will not be accepted for CATT.

The clinical center must have “dial-in” access to allow system vendors and Reading Center technical staff access to the system to trouble shoot and monitor performance.

### **8.2.2. Maintaining Digital System Certification**

The digital fundus cameras are certified at the beginning of the Study. The photographer is required to complete the CATT Digital Imaging System Information Questionnaire to inform the Fundus CATT FPRC of the form (digital or film) of photography to be performed and the digital systems available at the site. A Digital Imaging System Certification Form is required for each digital system to be certified to report the known hardware and software parameters. If at any time the certified fundus camera parameters set at the beginning of the Study don’t match with the parameters later in the Study, a warning will be issued. The CATT photographer will be notified to recalibrate the camera and submit a new CATT Digital Imaging System Certification Form.

### **8.3. TECHNIQUES FOR GOOD QUALITY IMAGES**

Note: Some of the instructions within Sections 8.3-8.5 are from *Digital Fluorescein Angiography Protocol, University of Wisconsin Fundus CATT FPRC (UW-FPRC) Digital FA module ver.4.1 (20May2004)*.

#### **8.3.1. Dilation**

Adequate dilation of the pupil is important to permit good quality stereo photography. Sufficient time should be allowed for dilation to *at least 6 mm*, repeating drops if necessary, to achieve and maintain a pupil of at least 6 mm during photography. If repeated instillation of drops and the passage of at least 45 minutes after the last drops fail to produce dilation of 6 mm, the photographs can be taken through a smaller pupil. If the pupil cannot be dilated to at least 4 mm, adequate stereoscopic effect may not be possible. The cornea should be undisturbed by prior examination with a diagnostic contact lens (Saine & Tyler, 2002).

#### **8.3.2. Stereopsis**

If it is not possible to obtain good quality (sharp focus) in both frames of the stereo pair, the photographer should attempt to obtain good quality in one frame and some stereo separation and accept poorer quality in the other frame. This may be the case if the eye has any media opacity. The aim should be to obtain some stereo separation between the members, accepting somewhat poorer quality in the second member of the pair if necessary.

***Sequence of Stereo Pairs for Digital Angiography and Color Photography:*** The frames of each pair should be taken in the order they will be viewed on the screen. Although the digital images can be viewed in any order chosen, with most systems it is more convenient (for both the photographer and the photograph reader) to take the left frame of the stereo pair first, followed by the right frame and thereafter alternating left frame, right frame. (See section 8.5.2)

***Sequence of Stereo Pairs on Film-based Angiography:*** The frames of each pair must be taken in the correct order for viewing directly on the film. The film should not have to be cut in order to view a pair in stereo. To achieve this, the angiogram should be taken in "reverse stereo", taking the right frame of the stereo pair first, followed by the left frame, thereafter, alternating right frame, left frame.

#### **8.3.3. Digital Image Resolution and Exposure**

All images acquired during angiography should be saved and sent to the CATT FPRC. Do not delete any images taken during the angiography sequence to submit only the recommended number of exposures or to remove images thought to contain objectionable artifacts. It is very important that photographers minimize flash/gain changes and avoid digital image overexposure, which can cause the areas of hyperfluorescence to appear artificially bright and possibly larger than they really are (sometimes referred to as blooming). A gain above 12db should not be used, to avoid grainy effects in the images.

Many digital cameras have a wider range of flash/gain settings available to control image exposure. Some photographers may frequently adjust the flash or gain settings during the angiogram to improve image quality. While this is often a useful adjustment, we do not want areas of hyperfluorescence to become overexposed. To safeguard against this, we recommend that photographers start the angiogram series using a flash setting that avoids overexposure, increasing the flash setting *only if several underexposed frames are observed*. This technique is preferred over starting the series with a flash setting that may be too bright and reducing it only if overexposure is observed.

*Image Modification:* Digital images must be acquired at the maximal resolution allowed by the camera. The original image acquired during the time of angiography should be stored on the local hard drive. Clinical center personnel should neither enhance (for example, modify brightness or contrast) nor compress the raw images. The images acquired during photography are to be identical to those transferred onto a CD-R for submission to the CATT FPRC.

#### **8.4. STANDARD FIELDS (Digital or Film)**

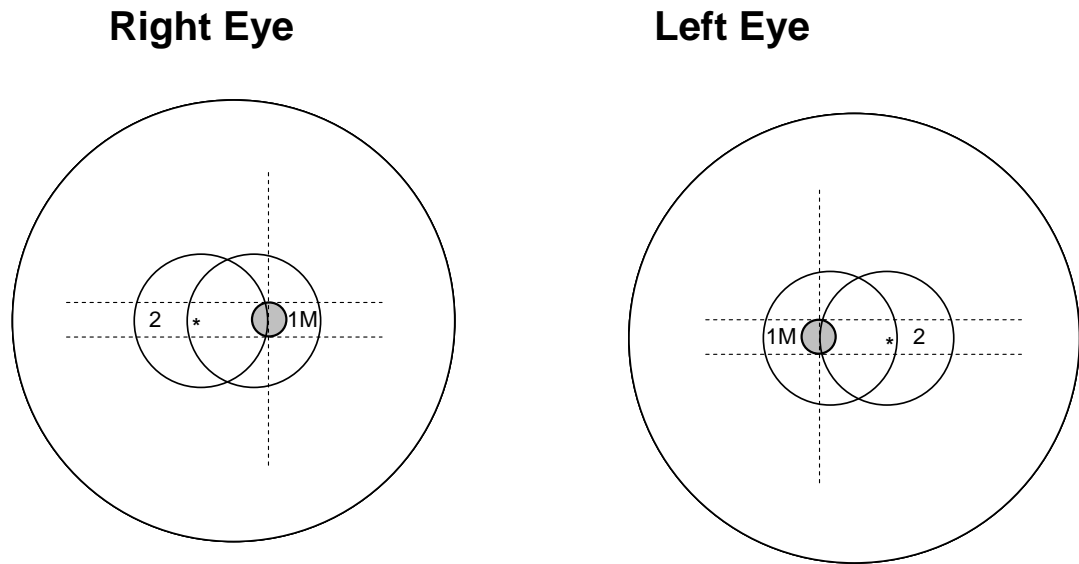
The required fields for CATT are Fields 1M and 2 (Figure 1).

The following descriptions of the standard fields assume that there are two cross hairs in the camera ocular, one vertical and the other horizontal intersecting in the center of the ocular.

**Field 1M – Disc:** Center the temporal edge of the optic disc at the intersection of the crosshairs in the ocular.

**Field 2 – Macula:** Center the macula near the intersection of the cross hairs in the ocular. To keep the central gray artifact created by some cameras from obscuring the center of the macula, the intersection of the cross hairs should be placed about  $1/8 - 1/4$  DD above the center of the macula. A suitable position can often be obtained by rotating the camera temporally from the Field 1M position, without vertical adjustment.

**Figure 1**



#### **8.4.1. Lesions that Extend Beyond Field 2**

When a neovascular lesion extends beyond Field 2, the photographer should attempt to obtain at least one stereo pair centered on the lesion to show its full extent. This stereo pair can be taken at any time during the angiogram that is most convenient for the photographer.

### **8.5. DIGITAL IMAGING**

**For required photography by Study visit see Exhibit 8-1.**

#### **8.5.1. Digital Color Photography**

The required fields for color photography are stereo pairs of fields 1M and 2.

#### **8.5.2. Digital Angiography**

The fluorescein angiogram contains stereoscopic views of 2 fields at specified times after injection (Exhibit 8-1). These fields include the macula (Field 2) of both eyes and a disc field (Field 1M) of the study eye. For Field 2, the camera should be centered near the center of the macula but not exactly on it, so that the artifact that is present in some fundus photographs will not obscure the center. In order to include all or most of the CNV lesion, the camera may be centered up to 2 DD from the center of the macula. In order to obtain stereo pairs that are correctly oriented on the computer monitor for stereo viewing (i.e. do not have reversed stereoscopic effect), the photographer must be careful to shoot the members of each stereo pair in the proper sequence. For example, OIS systems may arrange the images on the monitor in rows, starting in the upper right-hand corner and therefore it is best that the right member of each pair be taken first, followed by the left member, as you would if you were preparing a film-based fluorescein angiogram. However, IMAGENet<sup>®</sup> systems arrange the images on the monitor in rows, starting in the upper left-hand corner and therefore it is best that the left member of each pair be taken first, followed by the right member.

Stereoscopic red-free stereo pairs are taken of Field 2 in each eye prior to the injection of fluorescein dye.

Digital images are acquired at the maximal resolution allowed by the camera.

**Set-Up:**

- Excitation and Barrier Filters: 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 or any other time proves them to be defective.
- Red-free: A black and white red-free stereo pair of the both eyes is taken prior to fluorescein injection using a Spectratech 540 nanometer filter. The Kodak gelatin filter is not acceptable.
- Images should be stored on the computer at the maximum resolution of the camera and optical system in the loss-less “Bitmap or Tagged Image File Format (TIFF)” format.
- To avoid photographic artifacts, frequent inspection and cleaning of the front surface of the objective lens is essential to remove dust and debris.

**8.5.2.1. Fluorescein Injection**

After the stereo red-free photographs of Field 2 of both eyes have been taken, the camera is positioned for Field 2 of the study eye. Fluorescein is injected rapidly (less than 5 seconds) into the antecubital or other convenient vein according to usual clinic procedures.

**8.5.2.2. Timing**

**8.5.2.2.1. Early Phase:**

The first photograph of the early phase is taken at time “0”; that is, at the moment the injection of the fluorescein dye begins. The second photograph is taken at the moment the injection is completed. These photographs constitute a stereo pair and are referred to as the “control” photographs. They serve to document the integrity of the interference filters. The time shown on the second frame documents the rate of injection.

Ideally, the control photographs are followed by a series of 10-16 exposures taken at 1 to 2 second intervals, beginning about 15 seconds after the start of fluorescein injection (sooner if fluorescein appears sooner or delaying the initial exposures until fluorescence begins when a slow circulation time is expected). The usual result is 5 to 8 stereo pairs following the control pair, typically culminating about 40-45 seconds after the start of injection.

**8.5.2.2.2. Mid Phase:**

After the early photographs are completed the photographer take stereo pairs of Field 2 and then of Field 1M of the study eye at approximately 60-90 seconds. At this point the camera is positioned in front of the fellow eye and a stereo pair is taken of Field 2 at approximately 2 minutes. At this point, the camera is repositioned back to the study eye and a stereo pair of Field 2 is taken between 2 and 3 minutes.



### 8.5.2.2.3. Late Phase

A stereo pair of Field 2 in the study eye is taken at 5 minutes. Two final stereo pairs are taken of Field 2 in both eyes at 10 minutes.

### 8.5.3. Archiving, CD Preparation, CD Labeling

The image files of the entire angiogram and color photographs to be submitted for a trial are not to be compressed or altered in any way. In order to submit the images to the CATT FPRC, the image files must be copied to a CD-R for Study purposes only. If at the time of imaging the patient has not yet enrolled in the trial, the Study identification number and alpha code will not be available. The images are identified by the patient name from the images files at the clinical center. The Study identification number and alpha code are assigned to the images when images are transferred to the CD using the Submission Application. **To comply with HIPAA regulations, the patient's name should always be removed from the image files that are submitted to the CATT FPRC.**

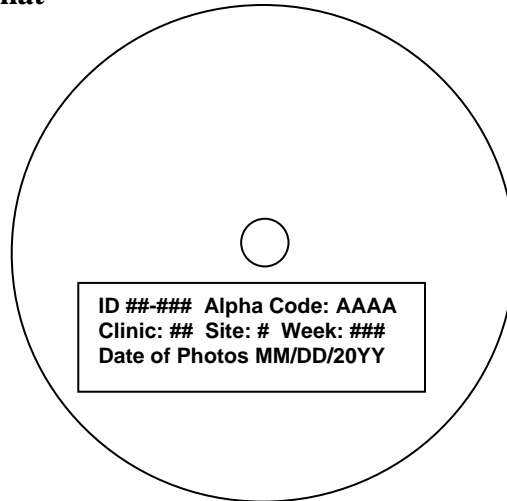
#### 8.5.3.1. Transfer of Digital Images to CD-R at the Clinical Center

The entire angiogram and color photographs should be written to a CD using only the custom developed software (Submission Application) distributed by the CATT FPRC for management of digital photographs. The graphical user interface allows the photographer to locate on the local computer and bring the previously stored digital images within the application environment on the screen. The incorporated conversion capabilities will recognize automatically the manufacturer of the digital fundus camera from the file format and it will convert it to a uniform, secure, lossless, storage image format. The photographer enters data in the fields provided (patient ID and alpha code) and selects the study eye, visit, photographer, and fundus camera type. Filtering capabilities will prompt the photographer for missing, or incomplete entries.

The Submission Application also will check for the image resolution, bit depth and other certified image parameters and it will warn if mismatch is encountered. Because angiography is performed prior to enrollment, digital image files may contain confidential patient information. The file name of each image from the image set will be replaced with the new name containing the patient ID, the order number of the picture in the set, and the date when the photograph was acquired. For the Topcon ImageNet™ generated image files the software will locate the patient name, if any, in the file header and will automatically delete it for masking, security, and confidentiality purposes. After the patient information is entered and verified the images are visually inspected. The image and data information is compiled in a single file and recorded on write once CD-R media. **Only one patient visit should be recorded on each CD.**

CD labels will be provided by the CATT FPRC that contain spaces for the patient ID number and alpha code, date of the angiogram and the Study visit identifier. The CD-R disk is placed in a protective sleeve and a CD mailer to protect the CD from damage in transit. The Clinic Coordinator submits the CD-R disk and the CATT Image Data Submission Sheet to the CATT FPRC according to the procedures detailed in Sections 8.7 and 8.8 below.

## CD Label Format



### 8.6. FILM BASED PHOTOGRAPHY

**Cameras:** The Zeiss 30° or Topcon 35° fundus cameras with 2.5X to 3X magnification should be used for both color photographs and fluorescein angiograms on film. Other cameras may be acceptable pending specific certification by the CATT FPRC.

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.

To avoid photographic artifacts, frequent inspection and cleaning of the front surface of the objective lens is essential to remove dust and debris.

#### 8.6.1. Required Fields

The required fields for film based photography are the same as for digital photography (See 8.4 Standard Fields).

#### 8.6.2. Film-Based Color Photography

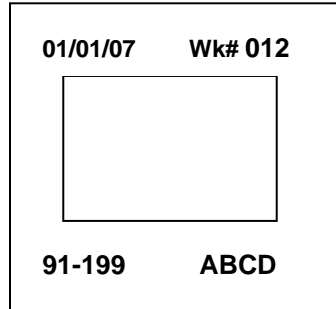
##### 8.6.2.1. Film and Film Processing

- The recommended films for color photography are Kodak Professional 100 daylight films or their equivalent. Ektachrome EPN, EPP, or E100S, preferably processed by a certified “Q-Lab” to ensure consistent quality, are preferred. Kodak Kodachrome 25 or 64 Daylight film, processed by any authorized Kodalux Laboratory is also acceptable.
- The processed film from Initial Visit photographs must be received at the CATT FPRC within 15 working days.
- Since there may be a slight difference in the color balance of different films, the CATT FPRC investigators recommend that whenever possible the same film type be used for all photographs for a patient.

### 8.6.2.2. Labeling and Presentation of Color Photographs

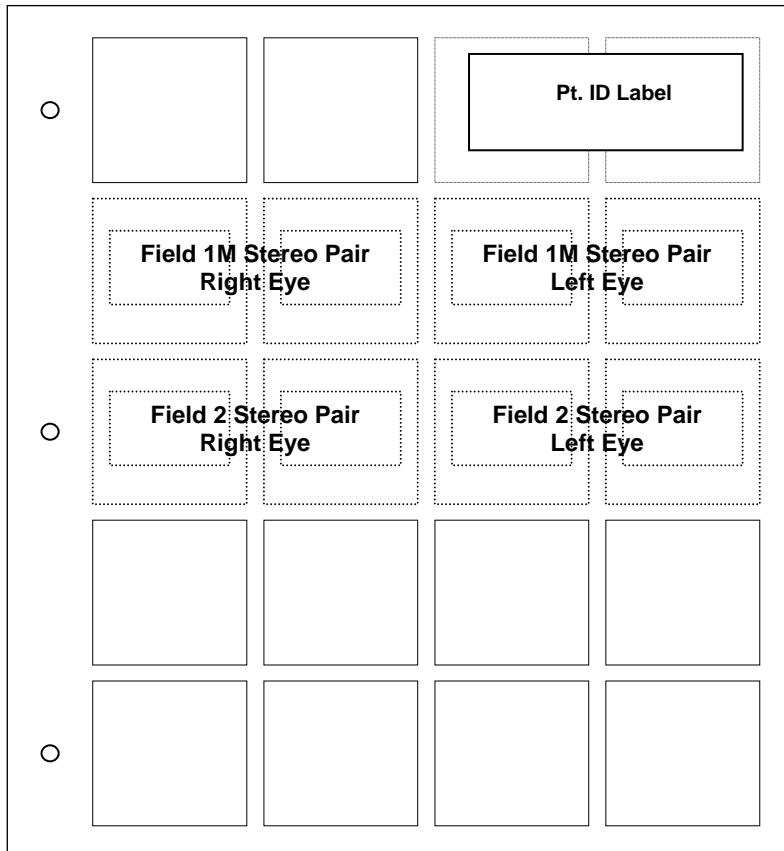
Color photographs from all visits must be labeled with the date of the photographs, and the visit number at the top of each slide mount, and the patient identification number and alpha code at the bottom of the slide mount. Patient-specific labels will be provided by the CATT Coordinating Center following randomization. If at any time these labels are not available, information should be printed on the slide mount as shown here.

#### Slide Mount Label Format



A complete set of color photographs will contain 4 stereo pairs, one pair of each disc and one pair of each macula. The slides are placed in the slide sheets in the following order:

#### Slide Placement Diagram



The slides are to be placed into a side-loading transparent slide sheet to allow for grading without removal from the slide sheet. Side-loading pockets on the slide sheets decrease the chance of slides slipping out of the slide pages because the slide mounts touch at the adjacent openings. The slide sheet should be oriented with the 3-hole punch on the left and the pockets opening from the front. Empty pockets in the slide sheet should not be cut off. One slide sheet should not contain photographs of more than one patient or photographs for more than one visit. To facilitate grading and filing of the photographs, a whole slide sheet should be submitted for each visit.

The patient ID label that contains the date of the photographs, the visit number, the patient identification number, and alpha code is placed in the upper right hand corner of the slide sheet to facilitate identification of the patient and visit.

### **8.6.3. Film-Based Fluorescein Angiography**

#### **8.6.3.1. Camera Equipment**

- 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 or any other time proves them defective.
- A Spectratech 540 nanometer filter is used for the black and white red-free stereo pairs taken prior to fluorescein injection. The Kodak gelatin filter is not acceptable.
- To avoid photographic artifacts, frequent inspection and cleaning of the front surface of the objective lens is essential to remove dust and debris.

#### **8.6.3.2. Film and Film Processing**

- Kodak T-Max, Tri-X, or Ilford 400 speed films are recommended for angiography. The film may be processed by clinic staff or at a local processing laboratory.
- Since the original angiogram negatives are submitted for reading, it is recommended that a high contrast developer be used to maximize capillary detail. Kodak D-11, diluted 1:1, should be used at approximately 70° for eight minutes or Kodak HC-110, dilution A, at 75° for six minutes. The exact processing time and temperature can be adjusted at the clinical center to compensate for differences in cameras and flash settings and to provide negative density acceptable to the CATT FPRC.

#### **8.6.3.3. Angiography Sequence**

The angiography sequence is the same as for digital angiography except for the order for stereo pairs. (See Section 8.5.2 for the angiographic timing and required fields and Section 8.3.2 for stereopsis)

#### **8.6.4. Labeling, Presentation, and Duplication of Film-Based Angiograms**

The patient ID label that contains the date of the photographs, the visit number, the patient identification number, and alpha code is placed in the upper right-hand corner of the negative sleeve. When more than one roll of film has been used and two negative sleeves are required, the first negative page should be labeled 1 of 2, and the second 2 of 2. As with the color photographs, patient-specific labels will be provided by the CATT Coordinating Center. If at any time these labels are not available, information should be printed on a label as shown below.

The roll of fluorescein negative images should be cut into 6 frames per strip and 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. If the protocol has been followed, i.e. the right side of the stereo pair is taken first, followed by the left side, thereafter alternating right side, left side, there will be three stereo pairs per strip of six images. When cutting the film into strips, the photographer should take care not to separate the members of a stereo pair, i.e., not to leave one member of the pair at the end of one strip and the second member of the pair at the beginning of the next strip.

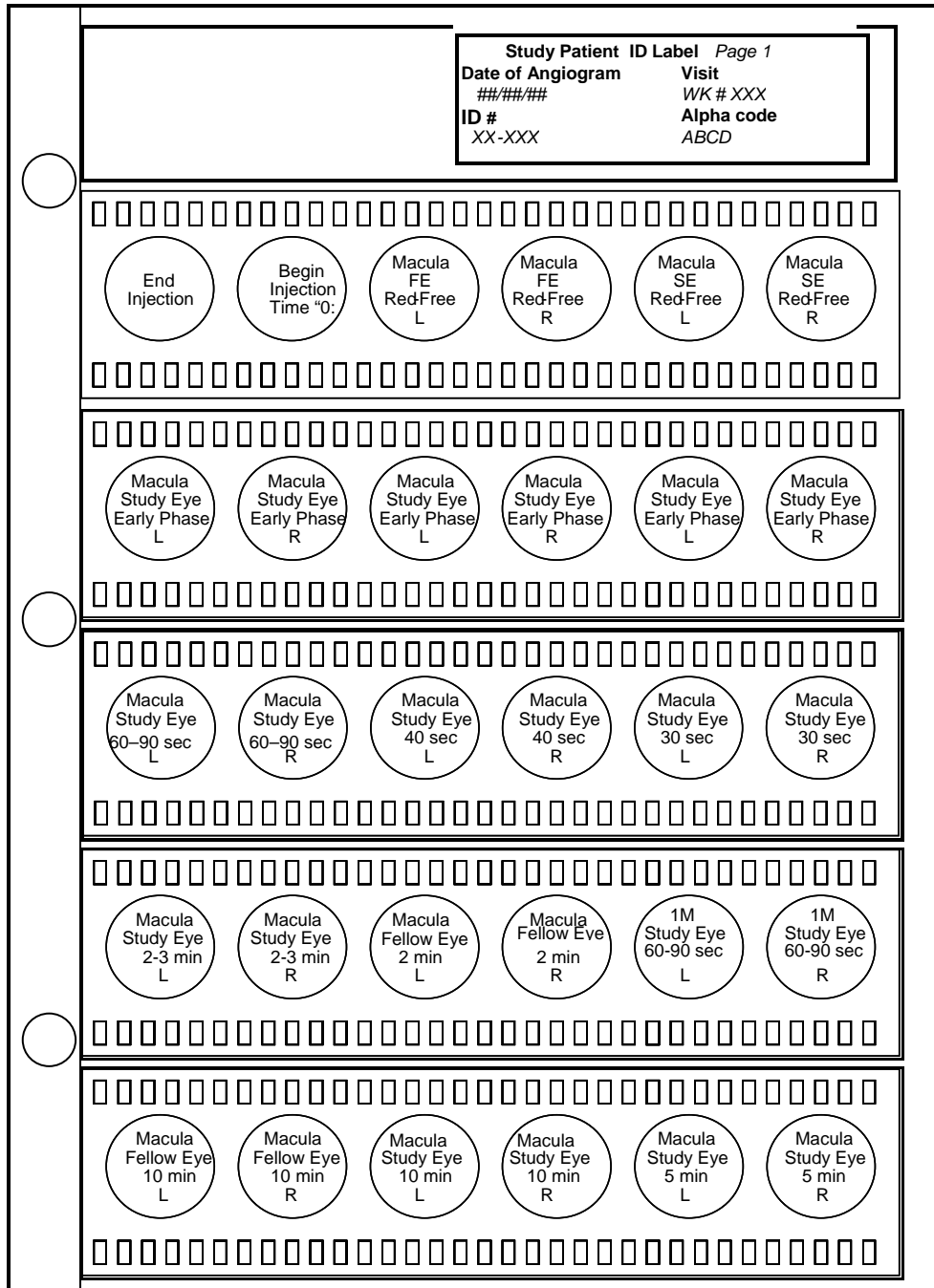
Blank frames should not be removed from the film. A second negative sleeve may be necessary to keep the pairs together. All frames of the roll of film should be submitted. If all the frames of the second roll of film are not used, include a few blank frames in the last strip of film to indicate the rest of the roll is blank. This is particularly important when the last frames were not taken at 10 minutes.

Do not staple the negative sleeves together.

**To comply with HIPAA regulations, the patient's name should always be removed from the film.**

A positive transparency or other form of duplicate angiogram should be prepared prior to submitting the negatives to the CATT FPRC. Negatives will not be returned to the clinical centers. If a copy is needed by a clinical center after submission to the CATT FPRC, a copy will be made by the CATT FPRC 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 due to adequate planning.

## Presentation of Fluorescein Film in Negative Sleeve



The sequence reads from right to left.

### 8.6.5. Modifications To Film Based Imaging Requirements

Acceptable results can be obtained with different development techniques and different films. Therefore, the following provisions are made for exceptions and revisions to this protocol.

If a CATT certified photographer at a clinical center believes that there is just cause for deviation from protocol, he/she may apply to the CATT FPRC for a variance. The application should include a letter of explanation, and several sample photographs produced by the proposed method. If the CATT FPRC agrees that the standards of CATT are upheld, the variance will be granted.

If the CATT FPRC staff identifies methods that they consider superior to those in use, those methods will be presented to the CATT Photographers for implementation.

## **8.7. READING CENTER FORMS**

### **8.7.1. CATT Image Data Submission Sheet**

The Image Data Submission Sheet is generated by the Submission Application and is submitted along with each set of digital photographs/angiograms submitted to the CATT FPRC. A second copy of the Image Data Submission Sheet should be printed and placed in the patient file at the clinical center. A set of photographs consists of both the required color photographs and the angiogram. The CATT FPRC Data Coordinator confirms the patient information with Coordinating Center data to ensure that the photographs are correctly identified for each patient visit. The Image Data Submission Sheet provides a means to log and track photographs received and provide information about the timeliness of the submission of materials. The Data Coordinator at the CATT FPRC documents on the form the date materials are received, if there are inconsistencies to be resolved, and the date the photographs are considered complete. The Image Data Submission Sheets are filed according to patient identification number in loose-leaf binders at the CATT FPRC.

If a printer is unavailable, a CATT Image Data Submission Form should be completed and submitted with the CD. This form is available on the CATT Remote Data Capture website.

### **8.7.2. Submission Log**

The CATT FPRC Submission Log is used to document materials included in a shipment to the CATT FPRC. A separate entry is made for each set of photographs submitted. One Submission Log is submitted per shipment. A copy is retained at the clinical center to identify any missing or partial shipments and to document that the materials have been sent. The CATT FPRC Data Coordinator confirms that the appropriate materials for patient visits listed are included in the shipment. The clinical center is notified whenever any materials are missing, incomplete, or enclosed but not indicated on the log. The CATT FPRC Submission Logs are filed in chronological order by receipt date by clinic in loose-leaf binders at the CATT FPRC. No data entry is performed for the CATT FPRC Submission Log. The Submission Log is available on the CATT Remote Data Capture website.

### **8.7.3. Incomplete Sets of Photographs**

A complete set of photographs consists of color photographs and a fluorescein angiogram. An incomplete set of photographs could occur when all required photographs are not taken or when photographs that were taken were subsequently lost, damaged, or misplaced. When not all of the required photographs are available for submission to the CATT FPRC, an explanation of the missing photographs should be included in the “comments” section of the Submission Log. This procedure is followed for film-based as well as for digital color photographs. Incomplete angiograms are identified at the CATT FPRC at time of receipt or during the grading process. An

explanation of an incomplete angiogram is not required on the Image Data Submission Sheet generated by the Submission application.

#### **8.7.4. Study Visits with No Photographs**

If all the required photographs (colors and angiogram) are not taken at a Study visit, or all of the required photographs taken at a visit are lost, destroyed, or misplaced, a Study Visit with Missing Required Photographs Form is still required. This form is available on the CATT Remote Data Capture website.

#### **8.7.5. Study Visits with Angiograms When Not Required**

Any time an angiogram is performed on a CATT study patient, it is submitted to the CATT FPRC in the same way as required photographs are submitted.

#### **8.7.6. Photograph Inventory Form for Film Images Only**

A Photograph Inventory Form for Film Images Only is submitted along with each set of photographs/angiograms submitted to the CATT FPRC. A set of photographs consists of both the required color photographs and the angiogram. The CATT FPRC Data Coordinator confirms the patient information with patient information from the Coordinating Center data to ensure that the photographs are correctly identified for each patient visit. This inventory form provides a means to log and track photographs received and provide information about the timeliness of the submission of materials. The Data Coordinator at the CATT FPRC documents on the form the date materials are received, if there are inconsistencies to be resolved, and the date the photographs are considered complete. The Photograph Inventory Forms for Film Images Only are filed according to patient identification number in loose-leaf binders at the CATT FPRC. This form is available on the CATT Remote Data Capture website.

#### **8.7.7. Photograph Inventory Form for Outside Visits**

A Photograph Inventory Form for Outside Visits is submitted along with any available photographs, either digital or film from an outside visit. The CD and/or photographs should be labeled following the same procedures for CATT Clinic visits. This form is available on the CATT Remote Data Capture website.

#### **8.7.8. Missed Study Visits**

When a patient misses a Study visit (time window has closed) nothing is submitted to the Reading Center. The information regarding missed visits is collected through the CATT Remote Data Capture website.

### **8.8. SUBMISSION OF MATERIALS TO PHOTOGRAPH READING CENTER**

All photographs, CD's, and other materials submitted to the CATT FPRC must be clearly labeled with the appropriate Study identification information and accompanied by a CATT Image Data Submission Sheet or appropriate Photograph Inventory Form, and Submission Log. 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 CATT FPRC 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.

CDs should be submitted in a protective sleeve and mailer. All photographs on film should be submitted in an envelope that is large enough to accommodate the slide pages and negative sleeves so that they are not folded or bent. Each shipment should include (Forms are available on the CATT Remote Data Capture website):

- Reading Center Submission Log- listing each patient visit
- CATT Image Data Submission Sheet or Photograph Inventory Form for Film Images Only- one for each patient visit
- Digital images copied to an appropriately labeled write-once CD placed in a protective sleeve and mailer
- Slides properly labeled and appropriately presented on the slide page
- Film-based angiograms appropriately labeled and presented in the negative sleeve
- Double-checked to be sure the patient's name does not appear on any of the materials submitted to the CATT FPRC

Copies of all forms should be retained at the clinical center in the Study files.

All materials should be shipped to:  
CATT Data Coordinator  
CATT Fundus Photography Reading Center  
3535 Market Street, Suite 700  
Philadelphia, PA 19104-3309

## **8.9. FUNDUS PHOTOGRAPH CONFIRMATION FORM**

A Fundus Photograph Confirmation Form will be issued whenever there is missing, discrepant, or incomplete information on the photographs, angiograms, or submission forms/logs,. This notice will be sent via FAX to the clinical center Coordinator identifying the problem, with instructions as to the resolution of the problem which could include resubmission of the images..

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 Fundus Photograph Confirmation Forms are responded to in a timely manner.

## **8.10. MONITORING PHOTOGRAPHIC QUALITY**

The quality of the focus/clarity and stereopsis of color photographs and angiograms is evaluated upon receipt at the CATT FPRC to monitor for problems or deviations from the photography protocol, missing photographs, and to provide timely feedback to photographers. Periodic reports

will be issued to the clinical centers summarizing image quality and identifying deficiencies that need attention.

## Exhibit 8-1

### CATT REQUIRED FUNDUS PHOTOGRAPHY Digital or Film

#### COLOR PHOTOGRAPHY (digital or film)

##### Baseline and all Follow-Up

Stereo pairs of field 1M and field 2 of both eyes.

#### ANGIOGRAPHY SEQUENCE (digital or film)

##### Baseline and Follow-Up (Sequence ALWAYS includes both eyes)

Phase	Field	Timing
Black & white Red-free 2 stereo pairs	Field 2 both eyes	Prior to dye injection
Control 1 <sup>st</sup> frame	Field 2 SE	Beginning of dye injection
Control 2 <sup>nd</sup> frame	Field 2 SE	Completion of dye injection
Early Phase 5-8 stereo pairs	Field 2 SE	Begin ~ 15 sec after the start of injection to 40-45 sec.
Mid Phase 4 stereo pairs	Field 2 SE Field 1M SE <i>Field 2 NSE</i> Field 2 SE	60-90 sec 60-90 sec 2 minutes Between 2 & 3 minutes
Late Phase 3 stereo pairs	Field 2 SE Field 2 SE <i>Field 2 NSE</i>	5 minutes 10 minutes 10 minutes

SE = study eye, NSE = non-study eye

#### REQUIRED PHOTOGRAPHY BY STUDY VISIT (Weeks)

	000	012	024	052	076	104
<b>Photography/Angiography*</b>	<b>X</b>	<b>S</b>	<b>S</b>	<b>X</b>	<b>S</b>	<b>X</b>

\*All photography/angiography is of both eyes

X: All patients

S: Substudy of 300 patients at selected centers (75 patients in each Study arm)

## CHAPTER 9

### PROCEDURES FOR OPTICAL COHERENCE TOMOGRAPHY

#### 9.1. INTRODUCTION

In response to the advances in Optical Coherence Tomography (OCT) imaging technology, the CATT study will accept three types of OCT images: Time Domain (TD) OCT using a Stratus OCT, and spectral domain (SD) OCT using a Cirrus or Spectralis OCT. Note that TD OCT must be used for all Subjects throughout the week 52 visit. Centers may choose to convert to SD-OCT imaging for Subjects who are completing visits beyond week 052, after certification for SD OCT has been obtained from the CATT OCT Reading Center.

Regardless of OCT type, a standard protocol will be followed by the clinical center technicians to obtain OCT scans from Subjects enrolled in the Study. Scans will be transferred electronically to the CATT OCT Reading Center (OCT RC). OCT technicians at the clinical centers must be certified by CATT (See Chapter 14, Clinical Center Staff Responsibilities and Certification Requirements) to obtain OCT scans of Study subjects.

Required clinic equipment and certification instructions for technicians wishing to be certified as a TD OCT technician on the Stratus OCT begin in section 9.2. Requirements and certification instructions for SD-OCT Technicians using the Cirrus OCT are discussed in sections 9.6 through 9.16. Requirements and certification instructions for OCT Technicians using the Spectralis OCT Machines are discussed in sections 9.17 through 9.21.

##### 9.1.1. Subject Confidentiality (all scan types)

All scans must be de-identified per established HIPAA guidelines. No identifiable personal data (not limited to name, subject initials, subject number, birthday, etc.) may be present on any material submitted.

##### 9.1.2. Schedule of Required OCT Scans

All Study subjects have OCT scans at weeks: 000, 004, 008, 012, 024, 052, 076, and 104. Study subjects on variable dosing have additional OCT scans at all other visits:

#### 9.2. TD-OCT REQUIRED EQUIPMENT

Stratus OCT with version 4.0 (or higher) software (for TD OCT)  
WinZip® software (available on-line at winzip.com)  
USB Printer Hub (required per Carl Zeiss Meditec)  
USB Drive  
Internet Access

##### 9.2.1. TD-OCT Required Maps

Stratus OCT will be used to obtain quantitative retinal thickness data and morphological cross-sectional information from subjects enrolled in the Study.

The Fast Macular Thickness Map and Macular Thickness Map acquisition functions will be used to obtain retinal maps.

Data will be exported to a USB device and then to another PC for transfer to the OCT RC via the Duke OCT Data Transmission Site (DTS). If the Stratus OCT is connected to the Internet and you have WinZip software on the Stratus OCT, you may transfer data from your Stratus OCT. WinZip (a zip file utility for Windows files) must be used to bundle the folder for transmission.

### 9.3. SUBMISSION OF CATT STUDY SCANS

#### 9.3.1. Required Data for each CATT Visit Requiring a TD- OCT:

- 1 Fast Macular Thickness Map (FMTM) OD
- 1 Fast Macular Thickness Map (FMTM) OS
  
- 1 Macular Thickness Map (MTM) OD
- 1 Macular Thickness Map (MTM) OS

**BEFORE** scanning any SUBJECT, the OCT technician must assign the **Subject ID number** for each Study Subject.

#### 9.3.2. Assigning Subject ID Information

For the initial study visit, use the information below for subject data entry. All **subsequent** study visits will use the same setup. **ALL FIVE DIGITS MUST** be entered for subject ID. This five-digit number is unique for each subject. The first two digits are unique to the clinical center. Digits 3-5 identify the subject number at the clinical center. **Without the first two digits this number will NOT be unique.**

In the **Last Name** field, enter the study name, **CATT**. In the **First Name** field, enter your site ID number & subject ID number. Do not use subject's first or last name.

At main OCT screen (**house icon**), click **eye icon** in upper left corner. Click **Add**.

**Last Name:** enter **CATT**

**First Name:** enter **XX-YYY**, where **XX is the site number, and YYY is the subject number**  
example: **75-100** (if your site number is 75 & your Subject ID is 100)

**Date of Birth:** enter **1/1/2001** for all Study Subjects (Real birthdates are not allowed.)

Click **OK**. Click **OK** at the bottom of the window.

Disregard all other fields for study subject entry. Subject is now coded and ready for study scanning.

#### 9.3.3. Data Export

##### Exporting Files to Desktop Folder

After all scans are obtained and ready for export/copy, follow these steps to export the files to the desktop folder:

Right click task bar and select “**Minimize All Windows**”. If unable to minimize, click the **X** icon in upper right corner of the home screen. Be advised that a long shutdown procedure may engage depending on system archive Preferences.

Right click the desktop. Click **New**. Click **Folder**.

Enter **CATT**, **Subject ID**, and **Visit #**. Click enter. This establishes a distinct folder from which the study subject’s scans can be exported and then transferred.

Re-open the Stratus OCT program by double clicking the **Stratus OCT Host** icon.

At the main menu (top of screen), click **Data**. Click **Export**. This starts the **Stratus Browser** program used for Database Export.

Enter **CATT** in the last name field. Enter the **CATT subject ID number** in the first name field; click **Search Now** (or simply scroll down subject list to find the subject number entry). Be advised that all study subjects will have the same “*last name*”, **CATT**. The subject number in the first name field will differentiate one study subject from the other.

Click the correct subject number (highlight) in the **Subjects** box on the left. Click the correct study scan date in the **Visits** box in the middle. Deselect unwanted visits, as there will be several after visits accumulate. Check the box next to the correct date. Note how all scans will now be checked in far right box. **There should only be four checked boxes** (1 FMTM and 1 MTM of each eye). Deselect any extra scans that are not needed for export such as non-protocol scans.

Click **File** in the upper left corner of the screen. Click **Database Export**. Click **Browse** to search for and select your distinct study folder on the desktop. Click and highlight the proper study folder in the directory. Click **OK**, **DO NOT** click the *Obscure Patient* box. Click **OK** in the bottom right corner.

Data will now be copied to the designated study folder on the desktop and an export confirmation window will pop up. Click **OK**.

Minimize all windows or close the **Stratus Browser** program by clicking on the **X** in the upper right corner. Stratus will return to the main OCT desktop.

When the folder is complete use Option A or Option B

**Option A** –Sites with Stratus OCT connected to the Internet **AND** WinZip on the Stratus OCT,

1. Right-click the folder and click **WinZip** from the menu.
2. Click **Add to Zip File**.
3. Select **None** for Compression.
4. Click **Add** in the upper right hand corner of the window.
5. Close the WinZip window.
6. File icon will appear on Desktop as a **WinZip vice** icon.

**Option B** - Sites with Stratus OCT **NOT** connected to the Internet **OR** that do not have WinZip on the Stratus OCT:

1. Copy folder to a removable USB device using the USB Hub (See below).
2. Upload the folder from the USB device onto an Internet-accessible PC with WinZip and copy the folder to the desktop.
3. **REMOVE** the USB device before zipping folder.
4. Right-click the folder and click **WinZip** from the menu.
5. Click **Add to Zip File**.
6. Select **None** for Compression.
7. Click **Add** in the upper right hand corner of the window.
8. Close the WinZip window.
9. File icon will appear on Desktop as a **WinZip vice** icon.

#### Stratus OCT Printer USB Hub instructions for Option B

1. Remove cord A from hub
2. Unplug printer cable from back of printer
3. Plug printer cable square end into square port on the back of the hub.
4. Plug rectangular end of cord A into any of the ports on the hub
5. Plug the square end of cord A into the back of the printer.

**Cord A**



**Hub**

#### 9.3.4. Data Transmission

A web-based Data Transmission Site (**DTS**) will be utilized to efficiently and securely transfer scan data from the clinical centers to the OCT RC.

##### **Instructions:**

Open your Internet browser.

Go to [www.dukeoct.org](http://www.dukeoct.org). Click the **Data Transmission Site** button on the left.

Log on to the **DTS** by entering your **User Name** and **Password**. These will be pre-assigned to each OCT technician by authorized personnel from the OCT RC.

Click the **Submit Scan** option on left. Select **CATT** from the scroll down menu in the **Study** box. Select **correct visit** in the **Visit** box. Select your clinical center in the **Site** box. Select **OCT** for scan type. Select technician's name in the **Technician** box. Check the **study eye** in the **Study Eye** box.

Next to the **Scan** box, click the **Browse** button. Browse to your desktop directory and select the zip file **CATT, subject ID #, visit #**. Double-click and highlight the zip file to be transferred. Enter any comments you think are necessary in the **Comments** box.

Click the **Submit** button at bottom left. Successful transmission will be indicated onscreen. Unsuccessful transmission will also be indicated onscreen. Please call or email the OCT RC to troubleshoot. See the CATT Study Registry for up-to-date contact information.

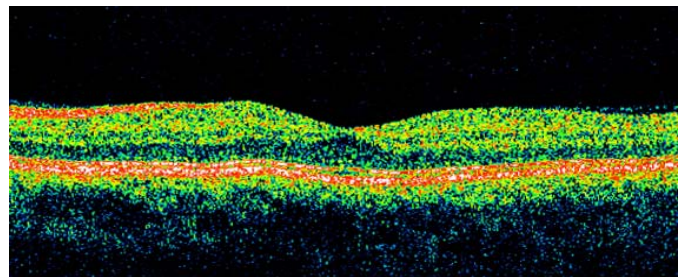
## 9.4. TD-OCT TECHNIQUE

### 9.4.1. TD-OCT Technical Considerations

The Stratus TD-OCT is an advanced modality that requires attention to detail to obtain the most accurate measurements achievable. Scan quality is essential in order for the analysis software to identify two key retinal layers, the Nerve Fiber Layer (NFL) and the Retinal Pigment Epithelium (RPE). Once these two layers are identified, the average retinal thickness and subsequent volume will be computed and rendered into a cubic millimeter calculation. Any one scan, not obtained correctly, can skew the volumetric reading even if the remaining scans in the group are of the desired quality. Therefore, each scan must be done correctly and accurately. Such skewing is usually obvious when the resulting retinal map contains pie-shaped scanning artifacts or atypical elevation spikes or depressions. (See Exhibit 9-1, Evaluation of Image Artifact Produced by Optical Coherence Tomography of Retinal Pathology)

The four key factors in obtaining accurate data are focus, scan saturation, line length, and line placement. When six radial scans are obtained incorrectly by focusing on the RPE, the resulting volumetric measurement may be incorrect as the computer may have difficulty rendering the upper NFL. Also, scan focus is important to image the vitreo-retinal interface to document presence of vitreous traction and/or detachment. There are some situations when it is not possible to obtain six high-quality radial scans on a given subject. NOTE: Do not attempt to image these subjects for certification. There will, however, be subjects enrolled in the study that will be difficult to scan. Edge to edge scan saturation should be dense and even for all six scans. The Fast Macular Thickness Map default length (6.0mm) is to be used for all Fast Macular Thickness Map scans. The Macular Thickness Map default length (6.0mm) is to be used for all Macular Thickness Map scans. Scan placement should include direct line placement through the fovea (joystick perpendicular to subject Module). At times, subjects may not be able to readily fixate on the green Fixation LED target.

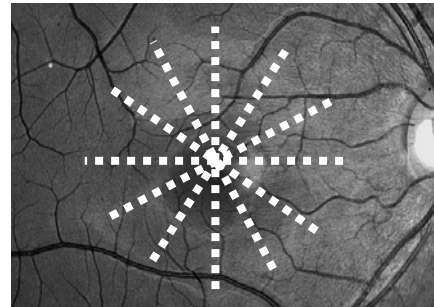
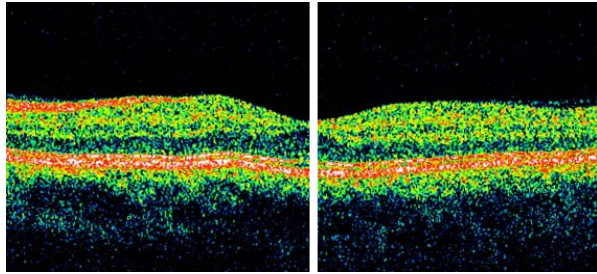
**Focus and Saturation:** With proper focus, discernable NFL and RPE and even color density and saturation along the length of the scan can be seen. Use *Optimize Polarization* function to ensure good saturation and focus. It is often unnecessary to focus using the focus knob on the Stratus OCT; the *Optimize Polarization* function typically provides good focus.



**Line Length:** With the Fast Macular Thickness Map mode and the Macular Thickness Map mode, six lines are scanned at default length (6.0mm) through the fovea. Scans should be level and square within the viewing window as pictured.



**Line Placement:** Initial preview *spinning array* and **Fixation LED** should be seen in the center of the viewing monitor. The radial scans pass through the fovea when proper placement is made. When scan is captured, use *freeze with flash*. The Stratus OCT allows users to project a white centering line through the middle of each active scan window. Users should use the line to center the fovea in each scan. It is enabled by clicking any active scan window during acquisition and can be turned on/off with mouse clicks.



#### 9.4.2. Scanning Problems/Difficulties

There will be occasions when quality retinal maps or scans cannot be obtained. The OCT RC at Duke provides consultation and advice for OCT technicians. Contact information is listed at the end of this document. Subjects who prove challenging should not be scanned for certification.

### 9.5. CERTIFICATION REQUIREMENTS TO PERFORM TD-OCT FOR CATT

#### 9.5.1. Overview

All TD-OCT Technicians must perform the following:

- Read specific chapters of the Study Manual of Procedures
- Complete the on-line CATT Study General Knowledge Assessment
- Complete the on-line OCT Technician Knowledge Assessment

In addition, TD-OCT Technicians **previously certified** by the OCT RC for submitting OCT scans **online** are required to Submit the *Request for OCT Certification Based on prior Certification Form*.

In addition, OCT Technicians **previously certified** by the OCT RC for submitting OCT scans **by CD** are required to submit one OCT image via the web-based Data Transmission Site (DTS) following the steps below.

In addition, **New** OCT Technicians must:

Submit scans of two subjects on the Stratus OCT and submit the scans to the OCT RC.

#### 9.5.2. Data Submission From Two Subjects For TD-OCT Certification

The specific scans to be performed on each eye include:

- 2 separate **Fast Macular Thickness Map (FMTM)** scan groups producing 2 distinct “Retinal Maps” of each eye
- 2 separate **Macular Thickness Map (MTM)** scan groups producing 2 distinct “Retinal Maps” of each eye

Summary of 16 certification scans of 2 subjects:

4 FMTMs per Subject:	8 Total
4 MTMs per Subject:	8 Total

**BEFORE** scanning any subject, you must:

1. Configure a Study Category on your Stratus OCT.
2. Assign the Study Category & Subject ID to that Subject.

### 9.5.3. Certification Subject Information Entry

**Subject Entry into OCT Database:** *For certification scans*, subjects must be de-identified and coded per this protocol.

At main OCT screen (**house icon**), click the **eye icon** in the upper left hand corner. Click **Add**.

**Last Name:** enter OCT technician's **Last Name** and **First Name**.

**First Name:** enter *Cert 1* & OCT technician's **First Name** and **Last Name**. Example: **Cert 1 johndoe**

**Date of Birth:** enter **1/1/2001**

Disregard all other fields for certification subject entry.

Certification scans can now be performed for Cert 1.

Repeat steps for Certification Subject 2 replacing **1** with **2** in proper fields.

### 9.5.4. Data Export for Certification

After all certification scans are obtained and ready for export/copy, follow these steps.

Right click task bar and select Minimize.

If unable to minimize, click the X icon in upper right corner of the home screen. Be advised that a long shutdown procedure may engage depending on system archive Preferences.

Right click on the desktop. Click **New**. Click **Folder**.

Enter OCT technician's **Last Name** and **First Name**, **Cert 1** and click enter. This establishes a distinct folder for the Study subject's scans to be exported and then transferred. Repeat the steps for the **Cert 2** folder, replacing **Cert 1** with **Cert 2**. This establishes two distinct folders for each certification subject to be exported. (OCT technicians currently certified with Duke only need one folder.)

Reopen the Stratus OCT program by double clicking on **Stratus OCT Host icon**.

From the main menu at the top of the screen, click **Data**. Click **Export**. This starts the **Stratus Browser** program used for Database Export.

Enter Certifying Technician's **Last Name** and **First Name** in the last name field near the top left. Then enter **Cert 1** (or 2) in the first name field. Click **Search Now** on left (or simply scroll down subject list to find the name).

Click the certifying technician's last name (highlight) in the **subjects** box on left. Click the scan date in the **Visits** box in middle. Check the box next to the date. Note how all scans will now be checked in far right box. There should be at least eight checked boxes (four FMTM and four

MTM). Unclick any extra scan boxes that are not needed for export. (For OCT Technicians currently certified, there should be at least one box checked.)

Click **File** in the upper left corner of the screen. Click **Database Export**. Click **Browse** to search for and select your distinct certification folder on the desktop. Click and highlight the proper certification folder in the directory. Click **OK**. **DO NOT** click the *Obscure Subject* box. Click **OK** in the bottom right corner.

Data will now be copied to the designated folder on the desktop and an export confirmation window will pop up. Click **OK**. The initial unzipped study folder must contain a *dataFiles* folder, a *transfer.ib* file and an *export* file.

Close the **Stratus Browser** program by clicking the **X** in the upper right corner. Stratus will return to the main OCT desktop.

When the folder is complete, use Option A or Option B below:

**Option A** –Sites with Stratus OCT connected to the Internet **AND** WinZip on the Stratus OCT:

1. Right-click the folder and click **WinZip** from the menu.
2. Click **Add to Zip File**.
3. Select **None** for Compression.
4. Click **Add** in the upper right hand corner of the window.
5. Close the WinZip window.
6. File icon will appear on Desktop as a **WinZip vice** icon.

**Option B - Sites with Stratus OCT NOT connected to the Internet OR that do not have WinZip on the Stratus OCT:**

1. Copy folder to a removable USB device using the USB Hub.
  2. Upload the folder from the USB device onto an Internet-accessible PC with WinZip and copy the folder to the desktop.
  3. **REMOVE** the USB device before zipping folder.
  4. Right-click the folder and click **WinZip** from the menu.
  5. Click **Add to Zip File**.
  6. Select **None** for Compression.
  7. Click **Add** in the upper right hand corner of the window.
  8. Close the WinZip window.
  9. File icon will appear on Desktop as a **WinZip vice** icon.
- Repeat the steps for the second certification set.

Stratus OCT Printer USB Hub instructions for Option B

1. Remove cord A from hub
2. Unplug printer cable from back of printer
3. Plug printer cable square end into square port on the back of the hub.
4. Plug rectangular end of cord A into any of the ports on the hub
5. Plug the square end of cord A into the back of the printer.



### 9.5.5. Data Transmission

This study will utilize a web-based Data Transmission Site (**DTS**) to efficiently and securely transfer scan data from the clinical centers to the OCT RC. To transmit data using the DTS perform the following steps:

Open your Internet browser.

- Go to **www.dukeoct.org** click onto the **Data Transmission Site** button on left.
- Log on to the **DTS** by entering your **User Name** and **Password**. These will be pre-assigned to each OCT technician by authorized personnel from the OCT RC.
- Click the **Submit Scan** option on left. Select the **DUKE** from the scroll down menu in the **Study** box. Select **Cert 1** in the **Visit** box. Select your site, in the **Site** box. Select technician's name in the **Technician** box. Select **OCT** for Scan Type. Check **both OD** and **OS** for certification submissions in the **Study Eye** boxes.
- Next to the **Scan** box, click the **Browse** button. Browse to your desktop directory and select the zip file of **Last Name – First Name, Cert 1**. Double-click and highlight the zip file to be transferred. Enter any comments you feel necessary in the **Comments** box.
- Click the **Submit** button at bottom left. Successful transmission will be indicated onscreen. Unsuccessful transmission will also be indicated onscreen. Please call or email the OCT RC to troubleshoot.

Please **WAIT** to see if transmission was successful.

Repeat same steps for the second zipped certification file. Select **Cert 2** in the **Visit** box for certification Subject two.

### 9.6. CONTACT INFORMATION

OCT RC  
2200 West Main Street  
Suite 930  
Durham, NC 27705

Phone: (919) 286-6575, (919) 286-6579  
Fax (919) 286-6586  
[www.dukeoct.org](http://www.dukeoct.org)

#### Helpful Hints

1. Get certified **immediately**.
2. Use same Subject ID for **First Name** and **Subject ID** on Stratus OCT.
3. Always **safely** eject USB drive before winzipping
4. Use **WinZip**.
5. Label Subject per protocol.
6. Use **ALL FIVE DIGITS** for Subject ID.
7. Call or e-mail for help.

## **9.7. SD-OCT TRANSITION PROCEDURES FOR SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY: CIRRUS**

### **9.7.1. CATT Mandates for Site Transition to SD-OCT**

1. The site is NOT to capture and submit any subject visit scans on an SD-OCT system until a technician from the site is certified on that SD-OCT system—prior to certification, all scans are to be captured on the Stratus OCT machine.
2. No SD-OCT scans are to be captured and submitted for any given subject until AFTER his or her week 52 visit has been completed.
3. The first **four** SD-OCT submissions during the transition are to be paired with Stratus OCT imaging of the same subject (per CATT OCT protocol) at each visit—in other words, dual system capture will occur for four sequential, scheduled subject visits.
4. After the full conversion from Stratus OCT to SD-OCT, the site is NOT to revert to Stratus (TD-OCT) for scan acquisition.
5. All of a subject's SD-OCT visit scans are to be captured on the same system, for every visit—sites are to select and use one machine (Spectralis or Cirrus) exclusively for a given subject.
6. After the transition to SD-OCT, all imaging continues on the same SD-OCT system through the completion of the study.
7. Per CATT protocol, both eyes are to be imaged per subject visit.

## **9.8. OVERVIEW OF CERTIFICATION REQUIREMENTS FOR CIRRUS SD-OCT TECHNICIANS**

### **9.8.1. Objective**

The purpose of this section is to describe:

- the protocol used by study-site technicians to obtain Cirrus HD-OCT scans from subjects enrolled in CATT
- the method used by study-site technicians to transfer scans electronically to the Duke Reading Center
- the method used by study site SD-OCT technicians to obtain SD-OCT scan certification for this clinical trial.

### **9.8.2. Subject confidentiality**

All scans must be de-identified per established HIPAA guidelines. No identifiable personal data should be present on any material submitted (not limited to name, birthday, etc).

### 9.8.3. Required equipment

Zeiss Cirrus HD-OCT with software version 4.0 or higher  
WinZip® software 8.0 or above (available on-line at winzip.com)  
USB Printer Hub  
Removable USB Drive (If Cirrus is not connected directly to the internet)  
Internet Access (use either Internet Explorer 6.0 or above or Firefox 1.5 or above)

### 9.8.4. Method

Zeiss Cirrus HD-OCT will be used to obtain quantitative retinal thickness data and morphological cross-sectional information.

A 512 x 128 Macular Cube and a 5 Line Raster scan group will be acquired per eye.

Data will be uploaded to the Duke Reading Center via the Duke Data Transmission Site (DTS) either directly from a Zeiss Cirrus computer that is connected to the internet or from another PC connected to the internet using a USB device to transfer the images from the Cirrus. If the Cirrus is connected to the Internet *and* you have WinZip software on the Cirrus machine, then you may transfer data from your Cirrus computer. WinZip (a zip file utility for Windows files) must be used to bundle the folder for transmission.

## 9.9. SPECIFIC CATT CIRRUS HD-OCT STUDY PROCEDURES

### 9.9.1. Cirrus HD-OCT study scans required for CATT

#### Data Submission for each visit:

1	512 x 128 Macular Cube OD
1	5 Line Raster OD
1	512 x 128 Macular Cube OS
1	5 Line Raster OS
4	<b>scan sets TOTAL per subject</b>

### 9.9.2. Subject information entry

Enter the subject's personal information as:

**Last Name:** CATT

**First Name:** XX-YYY, where XX=site number and YYY=subject number  
example: 75-100 (if site number is 75 and subject number is 100)

**Subject ID:** enter subject ID again (same as First Name— XX-YYY)

**Date of Birth:** enter 01/01/2001

- For the initial study visit, use the information above for subject entry. All subsequent study visits on the same instrument will not require additional subject information entry and should be acquired under this initial subject setup. ALL FIVE DIGITS MUST BE ENTERED for the First Name and Subject number fields. The five-digit number is unique

for each subject. The first two digits are unique to the clinical center. Digits 3 through 5 identify the subject at the clinical center. Without the first two digits, this number will NOT be unique across different clinics.

**Disregard all other fields for study subject information. Subject is now coded and ready for study scanning.**

## **9.10. PROCEDURE FOR IMAGING USING THE ZEISS CIRRUS HD-OCT**

### **9.10.1. Acquisition of images**

1. Select your subject from the Find Existing Subject tab or add subject using the Add New Subject tab. Click save after adding new subject.
2. Click Acquire to initiate the Acquire Screen. **Select the 512 x 128 Macular Cube for the eye to be scanned.**
3. Have the subject place his chin into the correct chin cup. Adjust table as needed.
4. Adjust image until pupil is centered, then, optimize and focus as needed.
5. Capture image- click the Capture button- then review and save or repeat imaging as necessary. If a scan has poor saturation or is of poor quality, have the subject blink or apply artificial tears, and repeat the scan. Submitted scans should be of the best possible quality.
6. **Select 5 Line Raster scan for the eye to be scanned.**
7. Capture, then review and save or repeat as necessary. If a scan has poor saturation or is of poor quality, have the subject blink or apply artificial tears, and repeat the scan. Submitted scans should be of the best possible quality.
8. Scan the other eye—have subject move to other chin cup. If Cirrus does not recognize that the subject has changed position, select the scan group from the appropriate eye menu at the top of the Acquire window.
9. Repeat steps 2-8 for this eye.
10. After all scans have been captured and saved, click the Finish button.

## **9.11. EXPORTING FROM THE ZEISS CIRRUS HD-OCT**

(Sites with internet access and WinZip software installed on the Cirrus may not need to perform the USB device steps)

1. Insert a USB removable drive such as a thumbdrive into the USB port in the front of the Cirrus instrument
2. From the home screen, select **Records** from the menu, then select **Export Exams** to open the **Export Options** dialog window.

3. Enter CATT in the Last name field and enter the Subject ID into the Subject ID field.
4. Click the Search button - this will display your subject and all visit dates. Cirrus 4.0 cannot export scans from a single visit date. Each export will contain ALL scans for that subject. Later versions of Cirrus software have the capability to export scans from a single visit.
5. In the upper portion of the same window, select the **Browse** button.
6. Find your USB device in the list. You may need to expand “My Computer” by clicking the “+” sign. Expand your USB device by clicking the “+” next to it in the list. Once it has expanded, select the destination folder for your export, or click the “Make New Folder” button in the bottom of the window to create a new folder for your export. Once the final folder destination is selected, click “OK”.
7. Highlight the exam to be exported. Click the Export button. Wait for the progress bar to complete.
8. Safely remove the USB device by left-clicking the removable device icon on the computer task bar. After completing the ‘Safely eject’ step, remove the USB drive from the USB port.

## 9.12. SUBMITTING CIRRUS HD-OCT SCANS USING THE DUKE DATA TRANSMISSION SITE (DTS)

### 9.12.1. Preparing folders for submission

**Option A** –Sites with Cirrus HD-OCT connected to the Internet **AND** WinZip on the Zeiss Cirrus machine may proceed to **step 4**.

**Option B** - Sites with Cirrus **NOT** connected to the Internet **OR** that do not have WinZip on the Cirrus:

7. Copy folder to a removable USB device. (*Instructions on previous page*)
8. Transfer the folders from the USB device onto the desktop of an Internet-accessible PC with WinZip.
9. **SAFELY** remove the USB device before zipping folders. Safely remove by selecting the ‘Safely Remove Hardware’ icon on the lower right corner of the desktop taskbar.
10. Right-click the folder and click **WinZip** from the menu.
11. Click **Add to Zip File**.
12. Select **None** for Compression.
13. Click **Add** in the upper right hand corner of the window.
14. Close the WinZip window after the green light has appeared in the lower right hand corner (almost immediate).
15. File icon will appear on Desktop as a **WinZip vice** icon. This is your zipped folder.

### 9.12.2. Data Transmission Site (DTS)



This study will utilize a web-based Data Transmission Site (**DTS**) to efficiently and securely transfer scan data from the study sites to the Duke Reading Center.

1. Open your Internet browser.
2. Go to **www.dukeoct.org**. Click the **Data Transmission Site** button on the left.
3. Log in to the **Data Transmission Site** by entering your **User Name** and **Password**. These will be pre-assigned to each OCT technician by authorized personnel from the Duke Reading Center. If you do not have an account with the Data Transmission Site, please contact the project manager (Contact Information p. 14) regarding new account creation.
4. Click the **Submit Scan** option on left. Select **CATT** from the scroll down menu in the **Study** box.
5. Select **Visit**. Select your **site**. Select **SD-OCT** for scan type.
6. Select **certified technician's name**. If your name is not in the drop-down box, please contact the project manager.
7. Enter **Subject Id**. *The subject ID will consist of a 2-digit site number and 3-digit subject number (please use the same subject ID formatting for all following study visits—for example, if subject is submitted as subject ID 99-999, all following submissions for this subject should be submitted under subject ID 99-999, and not 99999 or 99 999).*
8. Enter **date of visit**. Check off the **study eye**—this is the subject's study eye. It is **either OD or OS**, not both.
9. Next to the **Scan** box, click the **Browse** button. Browse to your desktop directory and select the zip file (please name as **CATT, subject ID, visit**). Click and highlight the zip file to be transferred. Click **Open**. Enter any comments you feel necessary in the **Comments** box—protocol deviations, required scans that were accidentally omitted, etc.
10. Click the **Submit** button at bottom left. Successful transmission will be indicated on-screen, in green font, at the top of the page. Unsuccessful transmission will also be indicated on-screen, in red font, at the top of the page. If a successful submission is reviewed by a project manager, and submission is not acceptable, the project manager will delete the submission. An e-mail notifying reason of deletion will be e-mailed to the submitter. Please note reason for submission rejection before contacting the Duke Reading Center. If you are still having difficulty, please call or email the Duke Reading Center to troubleshoot.

### 9.13. CIRRUS HD-OCT CERTIFICATION FOR CATT

#### 9.13.1. Cirrus HD-OCT certification scans required for CATT

SD-OCT scans from **two subjects**. **At least one** subject must have **neovascular AMD**.

**From each subject:**

##### **Subject 1**

- 1 512 x 128 Macular Cube OD
- 1 5 Line Raster per eye OD

- 1 512 x 128 Macular Cube OS
- 1 5 Line Raster per eye OS

**Subject 2**

- 1 512 x 128 Macular Cube OD
- 1 5 Line Raster per eye OD

- 1 512 x 128 Macular Cube OS
- 1 5 Line Raster per eye OS

8 Certification scans total from two subjects

**9.13.2. Certification subject information entry**

Last Name, First name and Date of birth are sufficient. All other fields may be left empty. Enter the subject's information as:

**Last Name:** enter Cirrus HD-OCT technician's **Last Name** and **First Name** example: DoeJohn

**First Name:** enter **Certification 1** for your first certification subject

enter **Certification 2** for your second certification subject

**Date of Birth:** enter 1/1/2001

**Disregard all other fields for study subject information.**

**9.13.3. Acquisition of certification images**

Obtain certification scans for both subjects per the study protocol on page 5.

After all certification scans are obtained and ready for export/copy, follow the steps below

**9.13.4. Exporting Cirrus HD-OCT scans**

(Sites with internet access and WinZip software installed on the Cirrus may not need to perform the USB device steps)

1. Insert a USB removable drive such as a thumbdrive into the USB port in the front of the Cirrus instrument
2. From the home screen, select **Records** from the menu, then select **Export Exams** to open the **Export Options** dialog window.
3. Enter your last name and first name into the Last name field. (enter the same way you entered it for step 6.2 on page 9)
4. Click the **Interval** button then enter the date of the visit into both the **From** and **Through** date fields.
5. Click the Search button- this will display your subject and the date with the study scans. Verify that the correct date is displayed.
6. In the upper portion of the same window, select the **Browse** button.

7. Find your USB device in the list. You may need to expand “My Computer” by clicking the “+” sign. Expand your USB device by clicking the “+” next to it in the list. Once it has expanded, select the destination folder for your export, or click the “Make New Folder” button in the bottom of the window to create a new folder for your export. Once the final folder destination is selected, click “OK”.
8. Highlight the exam to be exported, Click the Export button. Wait for the progress bar to complete.
9. Safely remove the USB device by left clicking the removable device icon on the computer task bar. After completing the ‘Safely eject’ step, remove the USB drive from the USB port.

#### 9.13.5. Preparing folders for submission

**Option A** –Sites with Cirrus HD-OCT connected to the Internet **AND** WinZip on the Zeiss Cirrus machine may proceed to **step 4**.

**Option B** - Sites with Cirrus **NOT** connected to the Internet **OR** that do not have WinZip on the Cirrus:

1. Copy folder to a removable USB device. (*Instructions in Exporting on previous page*)
2. Transfer the folders from the USB device onto the desktop of an Internet-accessible PC with WinZip.
3. **SAFELY** remove the USB device before zipping folders. Safely remove by selecting the ‘Safely Remove Hardware’ icon on the lower right corner of the desktop taskbar.
4. Right-click the folder and click **WinZip** from the menu.
5. Click **Add to Zip File**.
6. Select **None** for Compression.
7. Click **Add** in the upper right hand corner of the window.
8. Close the WinZip window after the green light has appeared in the lower right hand corner (almost immediate).
9. File icon will appear on Desktop as a **WinZip vise** icon. This is your zipped folder.

#### 9.13.6. Data Transmission Site (DTS)

This study will utilize a web-based Data Transmission Site (**DTS**) to efficiently and securely transfer scan data from the study sites to the Duke Reading Center.

1. Open your Internet browser.
2. Go to HU [www.dukeoct.org](http://www.dukeoct.org)UH. Click the **Data Transmission Site** button on the left.
3. Log on to the **DTS** by entering your **User Name** and **Password**. These will be pre-assigned to each OCT technician by authorized personnel from the Duke Reading Center.
4. Click the **Submit Scan** option on left. Select DUKE from the scroll down menu in the **Study** box. Select *correct visit*. Select your site. Select **SD-OCT** for scan type. Select *technician’s name*. Enter *Last name, first name cert 1* in the *Subject ID* box. (**Example Doe John, Cert 1**)

Enter the date you acquired the scans in the *date of visit* box. Check BOTH for study eye. (only check one study eye for study subjects).

5. Next to the **Scan** box, click the **Browse** button. Browse to your desktop directory and select the zip file **Last name, First name, cert 1 (Example: Doe John, Cert 1)**. Click and highlight the zip file to be transferred. Click **Open**. Enter any comments you feel necessary in the **Comments** box.
6. Click the **Submit** button at bottom left. Successful transmission will be indicated onscreen. Unsuccessful transmission will also be indicated onscreen. Please call or email the Duke Reading Center to troubleshoot.

Repeat steps for your Certification TWO submission.

## 9.14. CONTACT INFORMATION

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## 9.15. SD-OCT TRANSITION PROCEDURES FOR SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY: SPECTRALIS

### 9.15.1. CATT Mandates for Site Transition to SD-OCT

1. The site is NOT to capture and submit any subject visit scans on an SD-OCT system until a technician from the site is certified on that SD-OCT system—prior to certification, all scans are to be captured on the Stratus OCT machine.
2. No SD-OCT scans are to be captured and submitted for any given subject until AFTER his or her week 52 visit has been completed
3. The first **four** SD-OCT submissions during the transition are to be paired with Stratus OCT imaging of the same subject (per CATT OCT protocol) at each visit—in other words, dual system capture will occur for four sequential, scheduled subject visits.

4. After the full conversion from Stratus OCT to SD-OCT, the site is NOT to revert to Stratus (TD-OCT) for scan acquisition.
5. All of a subject's SD-OCT visit scans are to be captured on the same system, for every visit—sites are to select and use one machine (Spectralis or Cirrus) exclusively for a given subject.
6. After the transition to SD-OCT, all imaging continues on the same SD-OCT system through the completion of the study.
7. Per CATT protocol, both eyes are to be imaged per subject visit.

## **9.16. OVERVIEW**

### **9.16.1. Objective**

The purpose of this document is to describe:

- the protocol used by study-site technicians to obtain Spectralis SD-OCT scans from subjects enrolled in the CATT trial
- the method used by study-site technicians to transfer scans electronically to the Duke Reading Center
- the method used by study site SD-OCT technicians to obtain SD-OCT scan certification for this clinical trial.

### **9.16.2. Subject confidentiality**

All scans must be de-identified per established HIPAA guidelines. No identifiable personal data should be present on any material submitted (not limited to name, birthday, etc).

### **9.16.3. Required equipment**

- Heidelberg Spectralis SD-OCT with software version 5.1 or higher
- WinZip® software 8.0 or above (available on-line at winzip.com)
- USB Printer Hub
- Removable USB Drive (If Cirrus is not connected directly to the internet)
- Internet Access (use either Internet Explorer 6.0 or above or Firefox 1.5 or above)

### **9.16.4. Method**

Heidelberg Spectralis SD-OCT will be used to obtain quantitative retinal thickness data and morphological cross-sectional information.

A custom 20° x 20°, 49 Section Volume acquisition function will be used to obtain one set of High Speed scans per eye. A 7 Line preset scan will also be used to obtain one set of scans per eye.

Data will be uploaded to the Duke Reading Center via the Duke Data Transmission Site (DTS) either directly from a Heidelberg Spectralis computer connected to the internet or from another PC connected to the internet. The latter will require an intermediate step using a USB device to transfer the images from the Spectralis machine. If the Spectralis machine is connected to the Internet *and* contains WinZip software, you may transfer data directly from the Spectralis computer. WinZip (a zip file utility for Windows files) must be used to bundle the folder for transmission.

## 9.17. SPECTRALIS SD-OCT STUDY SCANS REQUIRED FOR CATT

### Data Submission for each visit:

- 1 20° X 20° High Speed Volume scan centered on the macula OD
- 1 20° X 20° High Speed Volume scan centered on the macula OS
  
- 1 7 Lines preset scan centered on the macula OD
- 1 7 Lines preset scan centered on the macula OS
  
- 4 scan sets **TOTAL per subject**

### 9.17.1. Subject information entry

Enter the subject's personal information as:

**Last Name:** CATT

**First Name:** XX-YYY, where XX=site number and YYY=subject number  
example: 75-100 (if site number is 75 and subject number is 100)

**Subject ID:** enter subject ID again (same as First Name— XX-YYY)

**Date of Birth:** enter 01/01/2001

For the initial study visit, use the information above for subject entry. All subsequent study visits on the same instrument will not require additional subject information entry and should be acquired under this initial subject setup. **ALL FIVE DIGITS MUST BE ENTERED** for the First Name and Subject ID fields. The five-digit number is unique for each subject. The first two digits are unique to the clinical center. Digits 3 through 5 identify the subject at the clinical center. Without the first two digits, this number will NOT be unique across different clinics.

**Disregard all other fields for study subject information. Subject is now coded and ready for study scanning.**

## 9.18. PROCEDURES FOR SD-OCT IMAGING USING HRA SPECTRALIS

### 9.18.1. Acquisition of 20°x 20° volume scan images

1. Prepare the device (headrest and camera).
  - Make sure camera head is pulled all the way back.
  - Clean camera chinrest and forehead rest.
  - Check that lens is clean.
  - Adjust table height and chinrest for the subject.
2. Prepare the subject.
3. Open the software and Acquisition Window.
  - Create or open the subject file, start a new acquisition.
  - Pre-set the default *Acquisition Parameters*.
  - Select an Acquisition mode using the filter lever and the control panel.

If a captured scan on the HRA Spectralis system is upside down relative to scanned eye, please capture another scan with attention to avoiding Subject movement towards the imager or joystick movement towards the Subject—these can result in flipped scans ).

4. Choose a fixation target (internal or external, via control panel).
5. Ask subject to put head on headrest.
6. Make sure canthus mark is at eye / canthus level.
7. Bring camera forward, align the camera with the eye to be scanned.

On the Touch Panel:

8. Activate “OCT” image mode using the control panel.
9. Activate “IR + OCT” image mode.
10. Activate the 20° field of view setting.
11. Activate the scan patterns by selecting “Volume” in the control panel.
12. Select the ‘More’ option.
13. Select “High Speed.” This may be the default, but it is important to check before scanning.

On the Computer screen:

14. Set the ART mean to 9 frames by sliding the ART bar.
15. Adjust the number of Sections (lines) to 49 by holding down the shift key and using the up and down arrows to adjust the number of scans to be set at 49.
16. Adjust the height of your scan pattern to 20° by using the left pointing arrow on your HRA keyboard.
17. On the touch pad, select “Acquire” and acquire SD-OCT scans. You have now acquired the macula scan set.
18. Save images.
19. Move camera backward and then over to the other eye to acquire images for the other eye.
20. On the touch pad, start camera.
21. Verify that ‘Volume’ is still selected. Select ‘Volume’ if it is not selected.
22. On the touch pad, select “Acquire” and acquire the Macula scan set. (Scan settings should stay the same at 20° X 20°, ART set to 9, 49 sections, and High Speed mode; If not, please correct the settings).
23. Save images.
24. Review scans for saturation and completeness. If a scan has poor saturation or is of poor quality, have the subject blink or apply artificial tears, and repeat the scan. Submitted scans should be of the best possible quality. Please note that allowable laser exposure is limited to 300 seconds per eye, so (meticulous) efficiency is important.

### **9.18.2. Acquisition of 7 line preset images**

On the Touch Panel:

1. Activate “OCT” image mode using the control panel.
2. Activate “IR + OCT” image mode

On the Computer screen:

3. Select “7 Lines” preset scan
4. On the touch pad, select “Acquire” and acquire SD-OCT scans.
5. Save images.
6. Review scans for saturation and completeness. If a scan has poor saturation or is of poor quality, have the subject blink or apply artificial tears, and repeat the scan. Submitted scans should be of the best possible quality. Please note that allowable laser exposure is limited to 300 seconds per eye, so (meticulous) efficiency is important.

### **9.19. EXPORTING SD-OCT VOLUME SCANS AS AN E2E FILE (SEPARATELY FOR EACH EYE)**

1. Create a folder on the desktop for your export:  
Right click the desktop. Click **New**. Click **Folder**.  
Name the folder **CATT, Subject #, Visit #**  
**Example: CATT, 12-001, Visit 1**

This establishes a distinct folder into which the study subject’s SD-OCT file can be exported and then transferred.

2. Return to the Heidelberg Eye Explorer with your subject visit open.
3. Select the CATT protocol-required SD-OCT scans that were taken during this patient visit that and right click.
4. Select “export”. The “export Options” window opens\*.
5. Select “Browse” to find the folder you created on the desktop.
6. Before you save the file, rename the exported file in the “File Name” field to match the folder name:  
**Example: CATT, Subject #, visit #**
7. Clicking on the “SAVE” button returns you to the “Export Options” window. Please review your entry fields. Click OK here if all the fields are properly entered with only study information and no personal subject information.

**You should now have one e2e file containing scans for both eyes.**

**\*Your HRA export function may be different if you have upgraded your instrument software to a later version.**

### **9.20. SUBMITTING SPECTRALIS SD-OCT SCANS USING THE DUKE DATA TRANSMISSION SITE**

**Please note that each SD-OCT submission should contain scans for both eyes at all visits—one submission should contain scans for both eyes.**



### 9.20.1. Preparing folders for submission

**Option A** – Sites with Heidelberg Spectralis connected to the Internet **AND** WinZip on the Heidelberg Spectralis, proceed to **step 4**.

**Option B** – Sites with Heidelberg Spectralis **NOT** connected to the Internet **OR** that do **NOT** have WinZip on the Heidelberg Spectralis, start at **step 1**.

1. Copy the folder to a removable USB device using the USB Hub.
2. Transfer the folder from the USB device onto the desktop of an Internet-accessible PC with WinZip.
3. **SAFELY** remove the USB device before zipping folders. Safely remove by selecting the ‘Safely Remove Hardware’ icon on the lower right corner of the desktop taskbar.
4. Right-click the folder and click **WinZip** from the menu.
5. Click **Add to Zip File**.
6. Select **None** for Compression.
7. Click **Add** in the upper right hand corner of the window.
8. Close the WinZip window.
9. File icon will appear on Desktop as a **WinZip vice** icon. This is your zipped folder.

### 9.20.2. Data Transmission Site (DTS)

This study will utilize a web-based Data Transmission Site (**DTS**) to efficiently and securely transfer scan data from the study sites to the Duke Reading Center.

1. Open your Internet browser.
2. Go to **www.dukeoct.org** . Click the **Data Transmission Site** button on the left.
3. Log on to the **DTS** by entering your **User Name** and **Password**. These will be pre-assigned to each OCT technician by authorized personnel from the Duke Reading Center.

*Submitting the first of the two zipped folders.*

4. Click the **Submit Scan** option on left.
5. Select **CATT** from the scroll down menu in the **Study** box.
6. Select **visit**.
7. Select your **site**.
8. Select **SD-OCT** for scan type.
9. Select **certified technician’s name**. If your name is not in the drop-down box, please contact the project manager.
10. Enter **Subject Id**. The Subject ID is the combination of a 2-digit site number, 3-digit subject number.

11. Enter **date of visit**.
12. Check the **study eye**—this is the subject’s study eye. It is **either OD or OS**, not both.
13. Next to the **Scan** box, click the **Browse** button. Browse to your desktop directory and select the zip **CATT, Subject #, Visit #**. Click and highlight the zip file to be transferred. Click **Open**. Click and highlight the zip file to be transferred. Click **Open**. Enter any comments you feel necessary in the **Comments** box—protocol deviations, required scans that were accidentally omitted, etc.
14. Submit the zip file containing the e2e file. This e2e file should contain the scans for both eyes.
15. Click the **Submit** button at bottom left. Successful transmission will be indicated on-screen, in green font, at the top of the page. Unsuccessful transmission will also be indicated on-screen, in red font, at the top of the page. If a successful submission is reviewed by a project manager, and the submission is not acceptable, the project manager will delete the submission. An e-mail notifying reason of deletion will be e-mailed to the submitter. Please note reason for submission rejection before contacting the Duke Reading Center. If you are still having difficulty, please call or email the Duke Reading Center to troubleshoot.

<b>Example subject 99-999, study eye OD, scans for OU for Data Trans. Site</b>	
--	--

Study:	CATT (CATT)
Visit:	064
Site:	99 (XXXXXX)
Image Type:	SD-OCT
Technician:	Doe, John
<b>Patient Id:</b>	<b>99-999</b>
Visit Date	01/01/2001
<b>Study Eye:</b>	<b>OD</b>

## 9.21. SD CERTIFICATION FOR CATT

### 9.21.1. SD-OCT Certification Scans required for CATT

SD-OCT scans from **two subjects**. **At least one subject must have macular pathology.**

**From each subject:**

**Subject 1:**

- 1 20° X 20° High Speed Volume scan centered on the macula OD
- 1 20° X 20° High Speed Volume scan centered on the macula OS
- 1 7 Lines preset scan centered on the macula OD
- 1 7 Lines preset scan centered on the macula OS

**Subject 2:**

- 1 20° X 20° High Speed Volume scan centered on the macula OD
- 1 20° X 20° High Speed Volume scan centered on the macula OS
- 1 7 Lines preset scan centered on the macula OD
- 1 7 Lines preset scan centered on the macula OS

**8 Certification scans total from two subjects.****9.21.2. Certification subject information entry**

Last Name, First name and Date of birth are sufficient. All other fields may be left empty. Enter the subject's personal information as:

**Last Name:** enter SD-OCT technician's **Last Name** and **First Name** example: DoeJohn

**First Name:** enter **Certification 1** for your first certification subject  
enter **Certification 2** for your second certification subject

**Date of Birth:** enter 1/1/2001

**Disregard all other fields for study subject information.**

**9.21.3. Acquisition of Certification images**

Obtain certification scans for both subjects per the study protocol on page 5-7.  
After all certification scans are obtained and ready for export/copy, the steps below.

**9.21.4. Exporting SD-OCT volume scans as an e2e file**

1. Create a folder on the desktop for your export:  
Right click the desktop. Click **New**. Click **Folder**.  
Name the folder **Last Name First Name, Cert 1, eye**  
**Example: Doe John, Cert 1 OD**

This establishes a distinct folder into which the study subject's SD-OCT file can be exported and then transferred.

2. Return to the Heidelberg Eye Explorer with your subject visit open.
3. Select one of the SD-OCT volume scans and right click.
4. Select "export". The "export Options" window opens.
5. Select 'Browse' to find your folder you created on the desktop.
6. Rename the export in the "File Name" field: Last Name, First Name, Cert 1, EYE.  
(Example Doe John, Cert 1 OD)
7. Then click the "Save" button.
8. This returns you to the "Export Options" window. Click OK here if all the fields are properly entered with only study information and no personal subject information.

You are now done exporting the e2e file for **one of the two eyes imaged.**

Repeat steps 1-7 for the other eye.

These steps will be repeated for your Certification Subject 2.

#### 9.21.5. Preparing folders for submission

**Option A** –Sites with Heidelberg Spectralis connected to the Internet **AND** WinZip on the Heidelberg Spectralis, proceed to **step 4**.

**Option B** - Sites with Heidelberg Spectralis **NOT** connected to the Internet **OR** that do not have WinZip on the Heidelberg Spectralis, start with **step 1**.

1. Copy both folders to a removable USB device using the USB Hub. (*See certification for Hub connection*)
2. Transfer the folders from the USB device onto the desktop of an Internet-accessible PC with WinZip.
3. **SAFELY** remove the USB device before zipping folders. Safely remove by selecting the ‘Safely Remove Hardware’ icon on the lower right corner of the desktop taskbar.
4. Right-click one of the two folders and click **WinZip** from the menu.
5. Click **Add to Zip File**.
6. Select **None** for Compression.
7. Click **Add** in the upper right hand corner of the window.
8. Close the WinZip window.
9. File icon will appear on Desktop as a **WinZip vise** icon. This is your zipped folder.
10. Repeat 4-9 for the second folder.

#### 9.21.6. Data Transmission Site (DTS)

This study will utilize a web-based Data Transmission Site (**DTS**) to efficiently and securely transfer scan data from the study sites to the Duke Reading Center.

1. Open your Internet browser.
2. Go to [www.dukeoct.org](http://www.dukeoct.org). Click the **Data Transmission Site** button on the left.
3. Log on to the **DTS** by entering your **User Name** and **Password**. These will be pre-assigned to each OCT technician by authorized personnel from the Duke Reading Center.

*Submitting the first of the two zipped folders.*

4. Click the **Submit Scan** option on left. Select **DUKE** from the scroll down menu in the **Study** box. Select *correct visit*. Select your site. Select **SD-OCT** for scan type. Select *technician’s name*. Enter

*Last name, first name cert 1, OD* in the *Subject ID* box. (**Example Doe John, Cert 1 OD**) Enter the date you acquired the scans in the *date of visit* box. Check the *eye* you are submitting.

5. Next to the **Scan** box, click the **Browse** button. Browse to your desktop directory and select the zip file **Last name, First name, cert 1, EYE (Example Doe John, Cert 1 OD)**. Click and highlight the zip file to be transferred. Click **Open**. Enter any comments you feel necessary in the **Comments** box. **Submit only one file for this eye.**

6. Click the **Submit** button at bottom left. Successful transmission will be indicated onscreen. Unsuccessful transmission will also be indicated onscreen. Please call or email the Duke Reading Center to troubleshoot.

7. Click the Submit option on left then repeat submission steps for the other eye.

**For this study, you will submit each eye separately, so there will be a total of 4 submissions for certification.**

## 9.22. CONTACT INFORMATION

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# Evaluation of Image Artifact Produced by Optical Coherence Tomography of Retinal Pathology

ROBIN RAY, BS, SANDRA S. STINNETT, DRPH, AND GLENN J. JAFFE, MD

• **PURPOSE:** To determine the frequency and type of optical coherence tomography (OCT) fast macular thickness map (FMTM) scan artifacts, and whether these artifacts depend on patient diagnosis, demographics, and ocular therapy.

• **DESIGN:** Retrospective observational case series.

• **METHODS:** Records from patients who underwent an ophthalmologic evaluation by a member of the Duke University Eye Center vitreoretinal faculty and had an OCT scan produced by the FMTM protocol between July 7, 2003 and July 31, 2003 were reviewed. The relationships between OCT scan artifacts and ocular diagnosis, ocular treatment, and patient demographics were determined. Logistic regression was used to relate OCT scan artifacts simultaneously with ocular diagnosis and treatment.

• **RESULTS:** Scans from 171 eyes were analyzed. Retinal scan artifacts, though not observed in normal eyes, were identified frequently in eyes with macular pathology ( $P = .049$ ). Artifacts were observed in 43.2% of all scans, and of these, an erroneous retinal thickness measurement was obtained in 62.2%. Six types of OCT surface map artifacts were observed. Of these, inner and outer retinal misidentification, degraded image artifact, and "off center" artifact were significantly associated with central thickness calculation errors ( $P < .001$ ). Neovascular age-related macular degeneration (AMD), full-thickness macular hole, and photodynamic therapy were all associated with increased artifact ( $P = .002, .022, \text{ and } < .001$ , respectively).

• **CONCLUSION:** Optical coherence tomography scan artifacts are seen surprisingly frequently, adversely affect retinal thickness measurements in a high proportion of cases, and are diagnosis-dependent. Recognition of these

artifacts will improve retinal thickness measurement accuracy, and will prevent faulty treatment decisions that are based on inaccurate retinal thickness measurements. (Am J Ophthalmol 2005;139:18-29. © 2005 by Elsevier Inc. All rights reserved.)

**O**PTICAL COHERENCE TOMOGRAPHY (OCT) IS A noninvasive imaging technique that uses low-coherence interferometry to create high-resolution (10 to 15  $\mu\text{m}$ ) cross-sectional and topographic images of any optically accessible tissue. Structures in the cross-sectional image are differentiated by their inherent light reflectivity and graphically displayed by the OCT software. Optical coherence tomography has been used increasingly to evaluate and manage a variety of retinal diseases. Indeed, at our institution, it has now supplanted fundus photography and fluorescein angiography as the most commonly performed method to image the retina. It is used to diagnose and guide treatment decisions in eyes with macular holes, vitreomacular traction, choroidal neovascularization, macular edema, and epiretinal membranes, among others.<sup>1-5</sup> It also has been used successfully to follow changes in macular pathology over time.

Optical coherence tomography has been especially useful in diagnosing and following macular edema over time.<sup>4,6-8</sup> Macular edema occurs in many different disorders including diabetic retinopathy, uveitis, vascular occlusive disease, age-related macular degeneration (AMD), and macular hole. Macular edema determined by OCT correlates well with visual acuity, and with leakage determined by fluorescein angiography.<sup>4,8-10</sup>

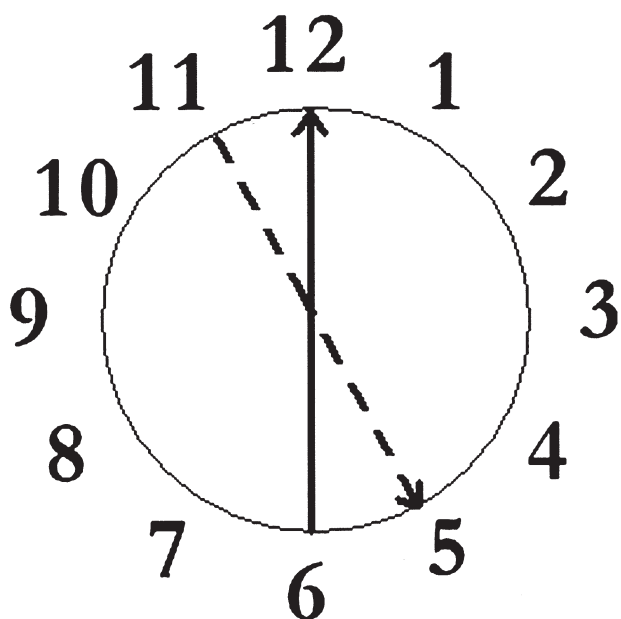
Many OCT scan modes are available to evaluate retinal pathology. However, in actual practice, only a few are used routinely. In particular, the Macular Thickness Map (MTM) scan mode and analysis function and the Fast Macular Thickness Map (FMTM) scan mode and analysis function on the commercially available Stratus OCT software (Carl Zeiss Meditec, Dublin, California) are used commonly to evaluate and follow retinal disorders. With these scan modes, six radial scans are obtained. In the MTM mode, each of the six individual sequential scans is

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**FIGURE 1.** Orientation of radial scans. Fast macular thickness maps can be graphically represented as a clockface. The origin of a cross-sectional retinal scan is at one of 12 clock hours and corresponds to the left-hand side of the cross-sectional scan. The end point of the scan is on the opposite side of the clock and corresponds to the right-hand side of the scan. For example, the solid arrow represents a cross-sectional retinal scan obtained from 6:00 to 12:00 meridian. The dashed arrow represents a cross-sectional retinal scan obtained from 11:00 to 5:00 meridian.

acquired manually by the operator, while in the FMTM mode, each of the sequential scans is obtained automatically by the OCT software. Each of the six scans is oriented radially, 30 degrees apart, and they intersect at the foveal center. Each radial scan (typically obtained at a scan length of approximately 6 mm) produces a cross-sectional image. Based on differences in the image reflectance patterns, the OCT software locates the inner retina at the vitreoretinal interface and the outer retina at the retinal pigment epithelial-photoreceptor outer segment interface. The software then places a line on the inner retina-vitreous interface and another on the retinal pigment epithelium (RPE)-outer retinal interface and determines retinal thickness as the distance between these lines at each measurement point along the scan's x-axis. From these scans, a surface-map reconstruction interpolated from the six radial scans is created. The surface-map is displayed as a false color image in which retinal thickness at each point is represented by a different color. Bright colors (for example, red and white) represent thick regions and dark colors (for example, blue and black) represent thin areas. Intermediate-thickness regions are displayed as green and yellow.

To accurately interpret morphologic topographic information and quantitative retinal thickness data produced by

the MTM and FMTM scanning modes, it is crucial to identify and, where possible, eliminate OCT scan artifacts. During the course of scanning patients in our clinic, we observed several different types of surface scan artifacts that could potentially influence retinal thickness measurements and have an adverse effect on therapeutic decisions. Some of these artifacts have been observed previously,<sup>11,12</sup> but none have been analyzed in a systematic manner. In this study, we determined the frequency of specific OCT scan artifacts and whether these artifacts affected the central retinal thickness measurement. We also determined whether particular artifacts were associated with patient demographic data, specific ocular and retinal diseases, and retinal disease therapy.

## METHODS

DATA WERE COLLECTED RETROSPECTIVELY FROM PATIENT medical records and the OCT scan database at the Duke University Eye Center. Institutional Review Board approval with a waiver of consent was obtained. Stratus OCT software was used to generate a list of patients who had an OCT examination in the desired time frame. Medical records from patients on this list were randomly selected for the study. Only patients who underwent an ophthalmologic evaluation by a member of the Duke vitreoretinal faculty and an OCT scan produced by the FMTM protocol between July 7, 2003 and July 31, 2003 were included. For every patient in the study, age, sex, race, physician, photographer, and OCT/physician visit date were recorded. The surface maps were graded as normal or abnormal by the first (R.R.) and third (G.J.J.) authors. A designation of "abnormal" was given to any map that deviated from the normal appearance of a central foveal depression (typically blue) surrounded by a slightly thicker macular region (typically appears green). If a foveal depression could be identified, but this contour was not centered on the surface map, it was graded as abnormal. When a surface map was graded as abnormal, each of the six radial scans used to create the surface map was analyzed to determine whether the abnormality was related to underlying retinal pathology or to a scan artifact. The orientation of the radial scans is described in Figure 1. The number of radial scans with a scan artifact, the specific type of artifact, and whether the artifact affected the calculated central thickness measurement were recorded. When scans were available from both eyes of a given patient, data from each eye were recorded and analyzed individually.

Once data from OCT scans of a particular eye had been collected, the medical record was used to record the clinical diagnoses for that eye, previous ocular surgical procedures, and ocular medical treatment (Appendix). Four diagnostic categories were created: macular diagnosis, nonmacular retinal diagnosis, nonretinal ocular diagnosis, and uveitis. Three therapeutic categories were created: macular treatment,

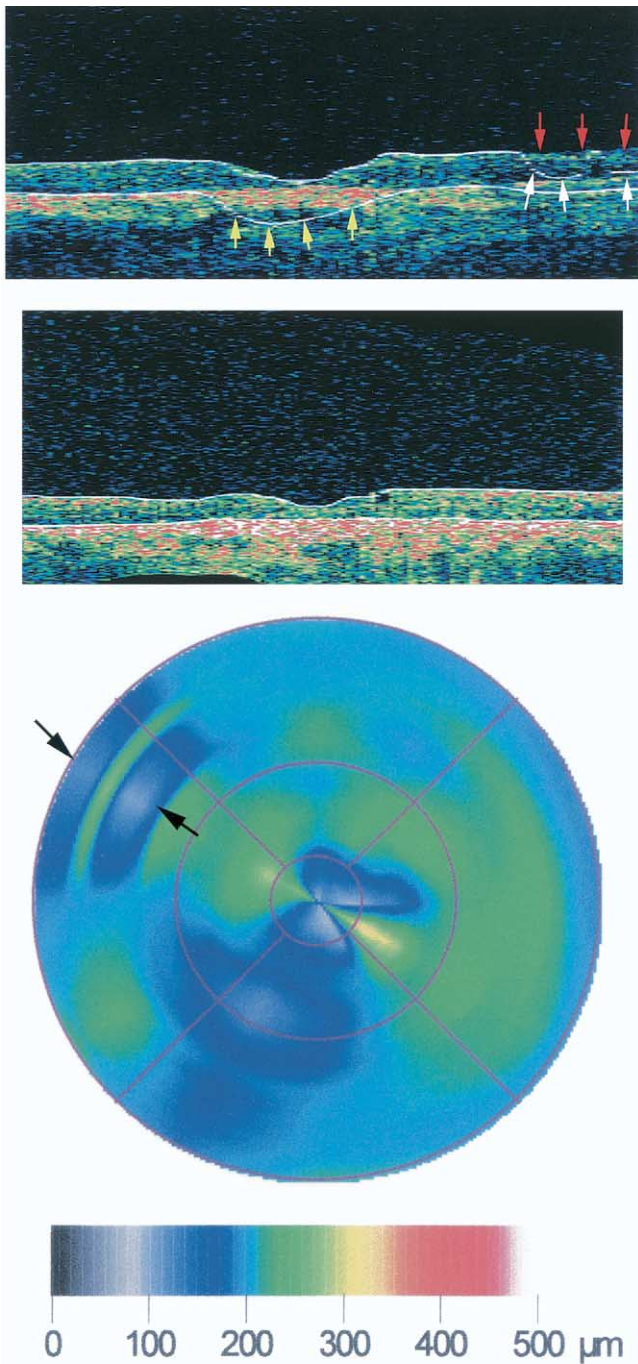


FIGURE 2. (Top) Cross-sectional retinal scan obtained from 4:00 to 10:00 meridian of a retina with neovascular age-related macular degeneration following photodynamic therapy for choroidal neovascularization. The optical coherence tomography software misidentified the inner retina on the right side of the image (white arrows). Red arrows correspond to true inner retina. Yellow arrows indicate an outer retina misidentification. (Middle) Representative cross-sectional retinal scan without artifact obtained from 6:00 to 12:00 meridian. (Bottom) Erroneous decreased thickness is observed at 10:00 meridian position on the retinal surface map (black arrows).

nonmacular retinal treatment, and nonretinal ocular treatment. All data were recorded in an electronic database. All patients were given identification numbers, and all patient identifiers were removed from the electronic database.

Frequencies and percentages were computed for all variables collected. A univariable analysis was conducted to determine whether there was a relationship between categorical variables (sex, age, and diagnosis) and presence of artifacts, whether specific types of artifacts caused a significant proportion of inaccurate central thickness measurements, and whether these particular types of artifacts were associated with specific ocular diagnoses. To assess the significance of these relationships, a  $\chi^2$  test or Fisher's exact test, as appropriate, was used. Two multivariable logistic analyses were conducted to determine whether particular demographic variables and ocular diagnoses were independently associated with the presence of artifact. For the first analysis, demographic variables (age and sex) and broad diagnostic categories were included in a logistic model. In the second analysis, demographic variables (age and sex) and diagnostic variables (neovascular AMD, posterior vitreous detachment (PVD), macular hole, choroidal neovascularization, and epiretinal membrane) were included in the model. To assess the simultaneous effects of several variables to presence of artifact, step-wise logistic regression was used. SAS/STAT 8 (Cary, North Carolina) was used for all analysis.

## RESULTS

• **DESCRIPTIVE VARIABLES:** The study comprised 171 eyes of 106 patients. Of these, 107 (62.6%) were female, and 151 (88.4%) were white. The mean patient age was  $67.2 \pm 15$  years. Of the total number of eyes observed, 87 (50.9%) were left eyes.

One hundred thirty-six eyes (79.5%) had one or more macular diagnoses, 51 eyes (29.8%) had one or more nonmacular retinal diagnoses, 86 eyes (50.3%) had one or more nonretinal diagnoses, 65 eyes (38.0%) had one or more macular therapies (medical or surgical), and eight eyes (4.7%) had nonmacular, retinal therapies. Thirteen eyes (7.6%) had uveitis, and 11 eyes (6.4%) were normal (normal eyes were defined as those with no eye disease on clinical examination, and no history of eye disease or treatment).

The most common diagnoses (those that were identified in more than six eyes), presented as (n, % eyes), were cataract (46, 26.9%), PVD (29, 17.0%), neovascular AMD (27, 15.8%), pseudophakia (27, 15.8%), macular edema not otherwise specified (26, 15.2%), epiretinal membrane (22, 12.9%), nonproliferative diabetic retinopathy with macular edema (22, 12.9%), nonneovascular AMD (20, 11.7%), increased intraocular pressure (12, 7.0%), retinal detachment (10, 5.8%), choroidal neovascularization not associated with AMD (9, 5.3%), subretinal fluid (9, 5.3%), and macular hole (8, 4.7%).



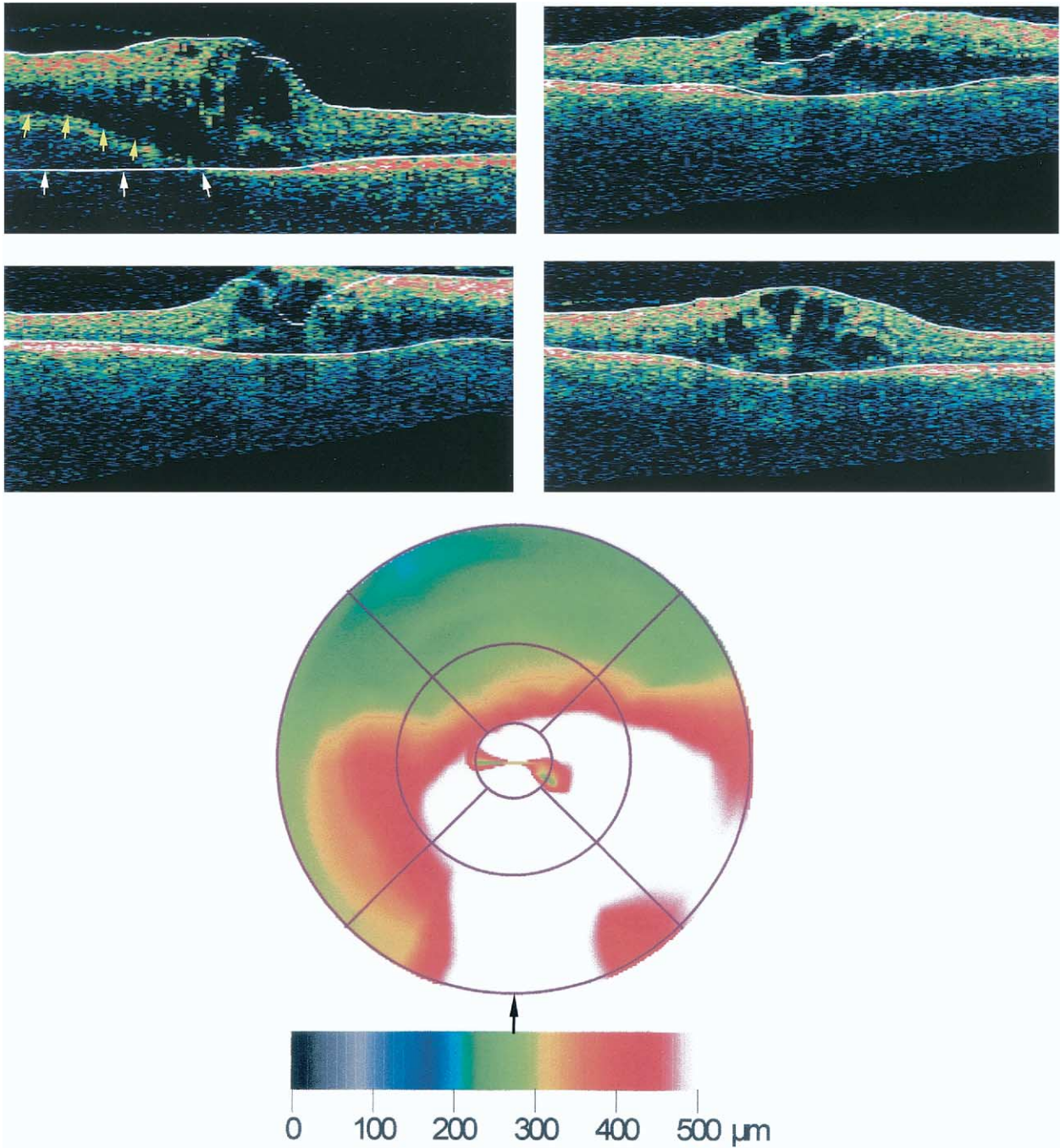


FIGURE 3. (Top Left) Cross-sectional retinal scan obtained from 6:00 to 12:00 meridian of a retina with macular edema caused by a hemiretinal vein occlusion. The optical coherence tomography software misidentified the outer retina on the left side of the image (white arrows). Yellow arrows correspond to true outer retina. (Top Right) Cross-sectional retinal scan obtained from 9:00 to 3:00 meridian with inner retina misidentification. (Middle Left) Cross-sectional retinal scan obtained from 10:00 to 4:00 meridian with inner retina misidentification. (Middle Right) Representative cross-sectional retinal scan without artifact obtained from 8:00 to 2:00 meridian. (Bottom) Erroneous increased thickness is observed at 6:00 meridian position on the retinal surface map (arrow).

Of the total number of surface maps (171) examined, 125 (73.1%) were abnormal. Of these abnormal surface maps, 71 (56.8%) contained one or more artifacts that contributed to the abnormality. The central retinal thick-

ness calculated by the computer was incorrect in 62.2% of eyes that had artifact in at least one of the six radial scans.

Six types of scan artifact were identified: (1) misidentification of the inner retina by the Stratus OCT

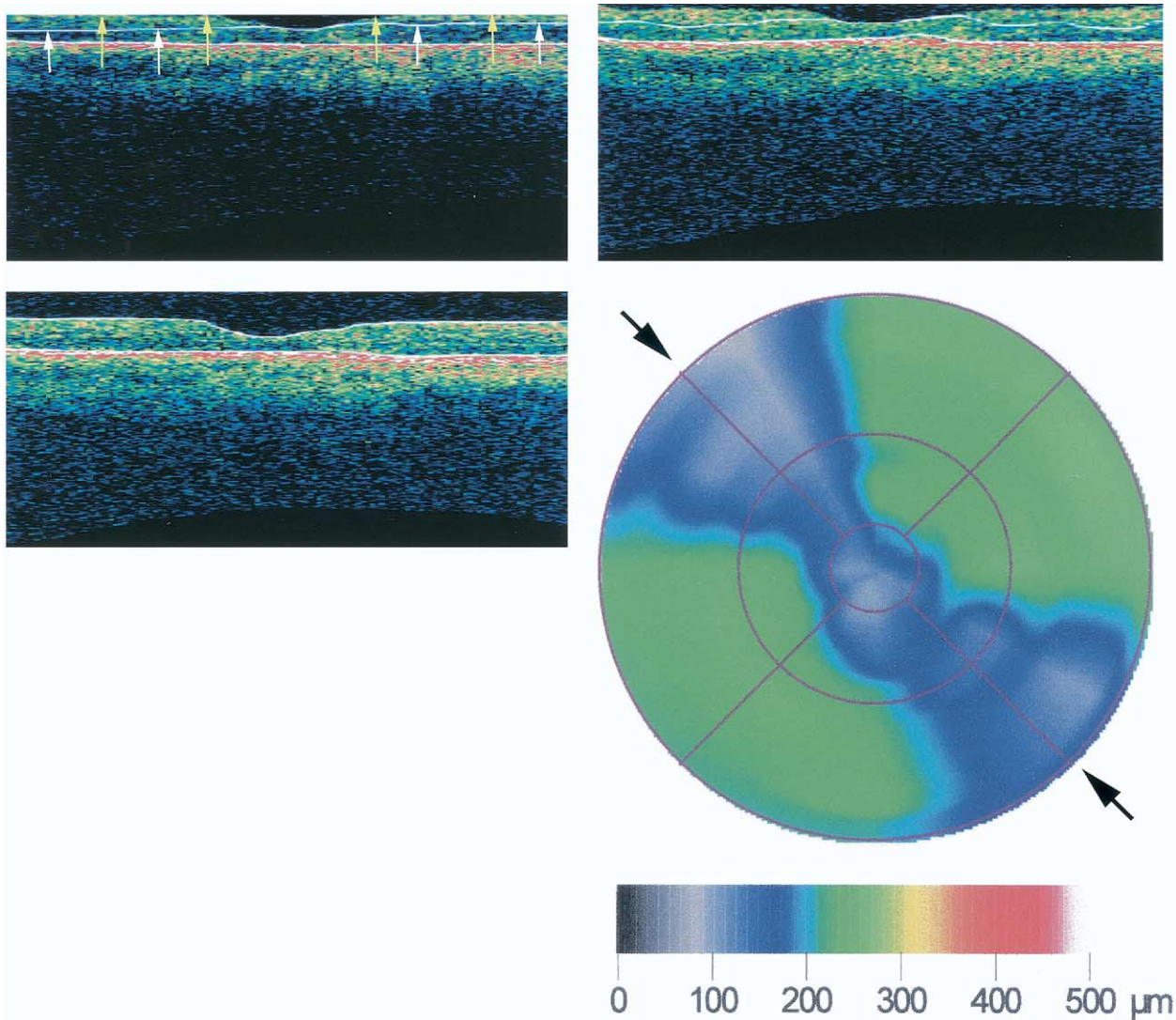


FIGURE 4. (Top Left) Cross-sectional retinal scan obtained from 11:00 to 5:00 meridian of a retina with age-related macular degeneration. The image is “out of register,” and the inner retina was misidentified (white arrows). Yellow arrows identify the true inner retina. (Top Right) Cross-sectional retinal scan with “out of register” artifact obtained from 10:00 to 4:00 meridian. (Bottom Left) Representative cross-sectional retinal scan without artifact obtained from 9:00 to 3:00 meridian. (Bottom Right) The blue area of the retinal surface map corresponds to a falsely thin area created by the “out of register” artifact (arrows).

software (Figure 2); (2) misidentification of the outer retina by the OCT software (Figure 3); (3) “out of register” artifacts, defined as a scan that was shifted superiorly such that the inner retina was truncated (Figure 4); (4) artifacts caused by a degraded scan image (Figure 5); (5) “cut edge” artifacts, defined as an artifact that occurred when the edge of the scan was truncated inappropriately (Figure 6); and (6) “off center artifacts” that occurred when the foveal center was misidentified (Figure 7). The inner retina was misidentified in one or more radial scans (of six) in 51 eyes (29.8%). The outer retina was misidentified in one or more radial scans (of six) in 41 eyes (24.0%). “Out of register” artifacts, degraded image artifacts, and “cut edge” artifacts occurred in one or more radial scans of six eyes (3.5%), 20

eyes (11.7%), and four eyes (2.3%), respectively. A foveal depression could be appreciated in 94 surface maps (55.0%). Of these, nine (9.6%) were “off center.” In the remaining 77 maps, a foveal depression could not be appreciated and no definitive determination of foveal centrality could be made.

Artifacts caused by limitations in the computer software identifying the retinal surfaces (inner and outer retina misidentifications and degraded image artifact) occurred in 61 (35.7%) of the surface maps. Artifacts derived from poor scan acquisition (“out of register,” “cut edge,” and “off center” artifact) occurred in 19 (11.1%) of the surface maps.

None of the scans of normal eyes had inner or outer retina misidentifications or degraded image artifacts. One

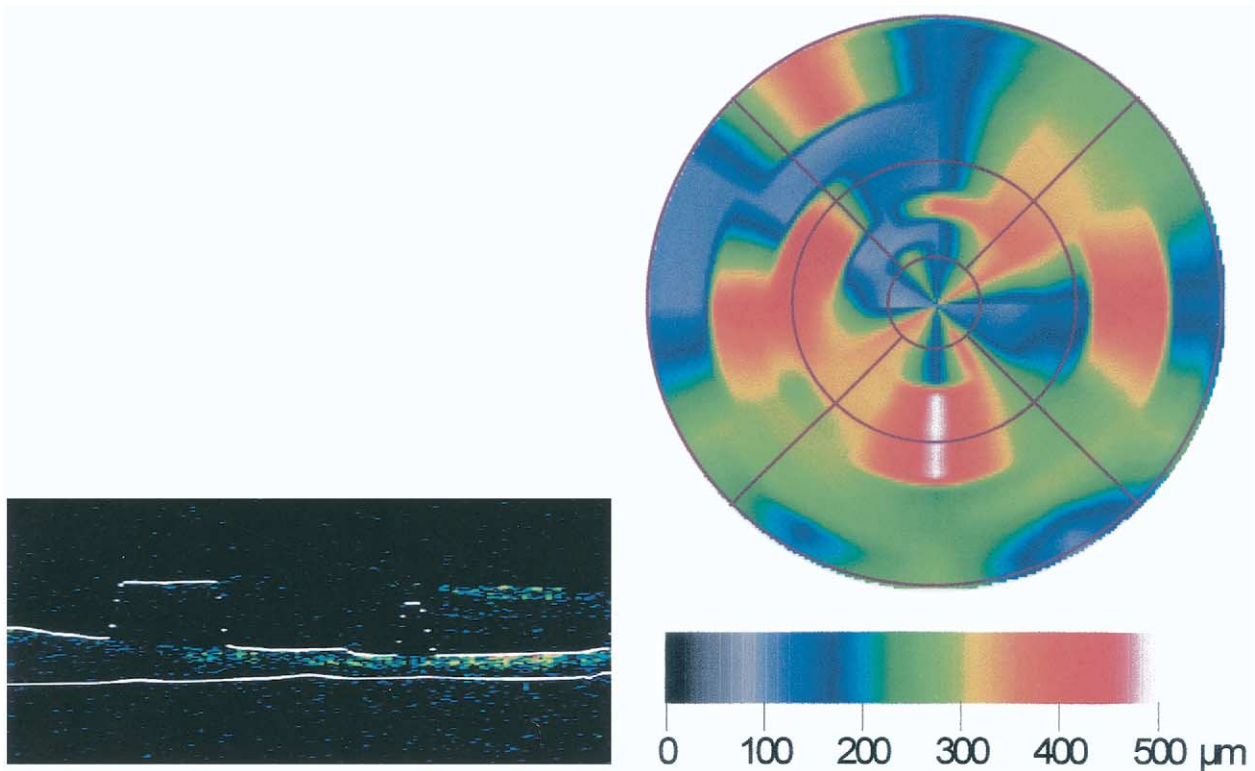


FIGURE 5. (Left) Representative cross-sectional retinal scan obtained from 6:00 to 12:00 meridian of an eye with dense cataract. Retinal details are not visible. The degraded image makes it impossible for the computer software to identify either the inner or outer retina. (Right) No useful data concerning retinal morphology or central foveal thickness can be obtained from the retinal surface map.

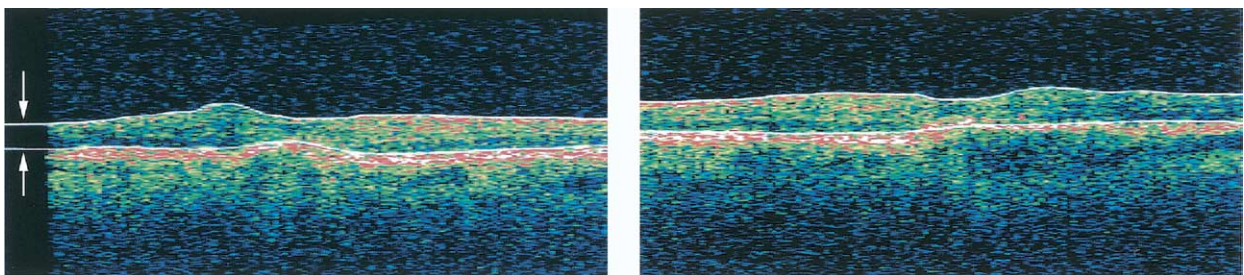


FIGURE 6. (Left) Cross-sectional retinal scan with a “cut edge” artifact (arrows) obtained from 6:00 to 12:00 meridian. Artifact may cause peripheral surface map artifact, but not inaccurate central retinal thickness measurements. (Right) Representative cross-sectional retinal scan without artifact obtained from 11:00 to 5:00 meridian.

of the scans in this subset had a cut-edge artifact, and two of the surface maps in this subset were off center.

- **UNIVARIABLE ANALYSIS:** Artifact occurred significantly more frequently in eyes with macular diseases than those without (Table 1). Eyes with neovascular AMD and full-thickness macular hole were especially prone to OCT artifact (Table 2). Similarly, eyes that had undergone photodynamic therapy for choroidal neovascularization were more likely to produce artifacts than those that had not been treated in this manner.

Specific types of artifacts were also associated with particular ocular diseases. Artifacts produced by misidentification of the inner retina occurred significantly more frequently in eyes with neovascular AMD, full-thickness macular hole, or those that had undergone photodynamic therapy, than in eyes without these diagnoses or therapy (Table 3). The inner retina was misidentified significantly more frequently in eyes with a nonretinal diagnosis than in those without nonretinal diagnosis (Table 1).

Artifacts produced by misidentification of the outer retina occurred significantly more frequently in eyes with

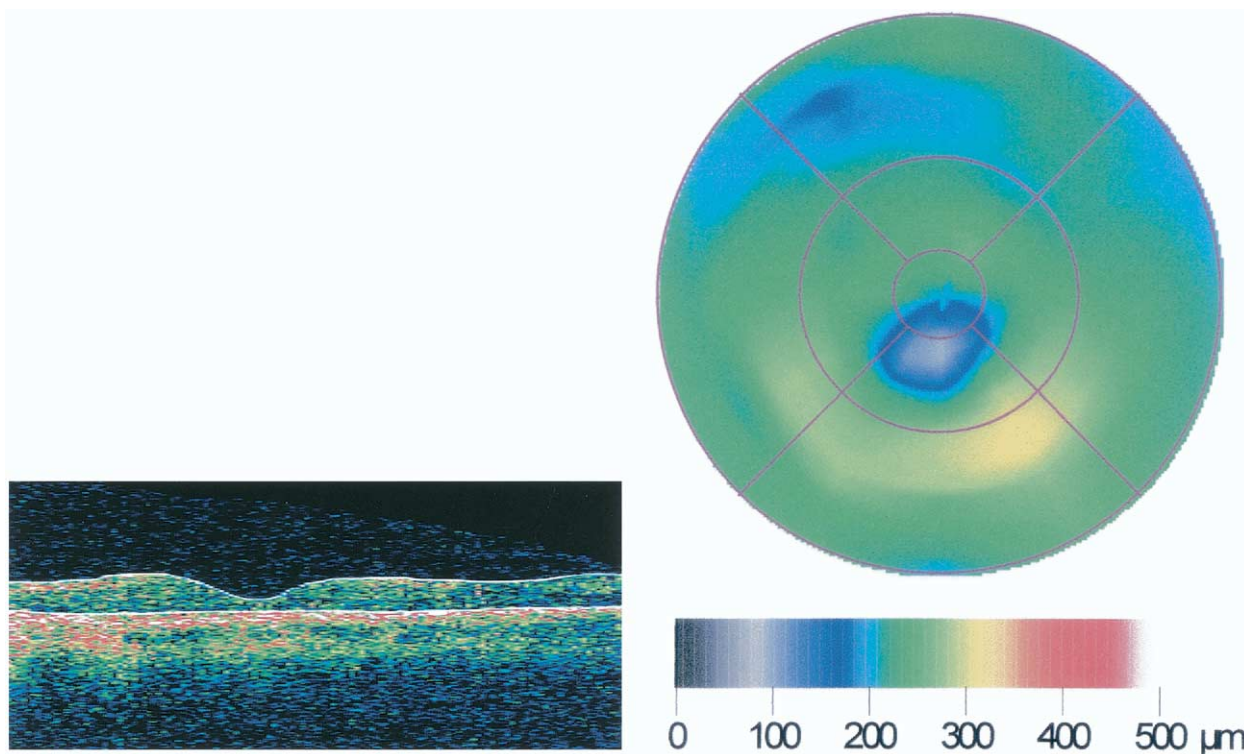


FIGURE 7. (Left) Cross-sectional retinal scan with normal appearing foveal depression obtained from 6:00 to 12:00 meridian. (Right) Surface map of a retina with “off center” artifact. The calculated central retinal thickness measurement will be inaccurate.

macular disease. In particular, it was significantly more common in eyes with neovascular AMD and those with choroidal neovascularization not associated with AMD than eyes without these diagnoses. It was also significantly more frequent in eyes with PVD and those that had undergone photodynamic therapy (Table 1 and Table 4).

Degraded image artifacts occurred more frequently in eyes having one or more nonretinal ophthalmic diagnoses than in those without. Although eyes with cataracts had degraded image artifacts more frequently than those without, the difference was not statistically significant (Table 5).

Although occurring less frequently than inner and outer retinal misidentification, “off center” artifacts were also significantly associated with a particular ocular diagnosis. “Off center” artifact occurred more frequently in eyes with neovascular AMD than in eyes without this diagnosis (4/12 [33.3%] vs 5/82 [6.1%],  $P = .014$ ).

In contrast with other types of artifacts, “out of register” and “cut edge” artifacts were not seen more frequently in diseased eyes than normal eyes under any conditions.

Particular types of OCT artifacts frequently caused the computer software to calculate central retinal thickness erroneously. Artifact caused by computer software misidentification of the inner and outer retina and degraded images all were significantly associated with an incorrect central retinal thickness measurement thickness, while an

“off center” artifact always produced an incorrect thickness measurement ( $P < .001$ ). These central thickness measurements were also affected by certain diagnoses. Central thickness measurements were affected by artifact more frequently in eyes having one or more macular diagnoses than those without (43/136 [31.6%] vs 3/35 [8.6%],  $P = .023$ ).

• **MULTIVARIABLE ANALYSIS:** Based on univariable analysis results, a multivariable analysis was conducted to determine whether particular types of artifacts were more commonly associated with broad categorical diagnoses, treatments, and the demographic variables sex and age when analyzed simultaneously (Table 6). For each of the artifacts evaluated, it was seen that certain variables were significantly related to the presence of the artifact. Outer retina misidentifications were significantly related to macular diagnoses, and degraded images were significantly related to nonretinal diagnoses. Inaccurate center thicknesses were significantly associated with macular diagnoses and nonretinal diagnoses. “Out of register” artifact, “cut edge” artifact, and “off center” artifact were not significant and are left out of the multivariable tables.

In the second multivariable analysis relating specific diagnoses and demographic variables to the presence of artifact (Table 7), several diagnoses that were found to have a significantly increased artifact frequency in the

**TABLE 1. Univariable Analysis of Categorical Diagnoses\* and FMTM Radial Scan Artifact**

Categoric Diagnosis	Number (%) With Any Artifact	P Value <sup>†</sup>	Number (%) With IRM	P Value	Number (%) With ORM	P Value
Macular diagnosis		.049		0.066		.017
Yes	64/136 (47.1)		45/136 (33.1)		38/136 (27.9)	
No	10/35 (28.6)		6/35 (17.1)		3/35 (8.6)	
Nonmacular retinal diagnosis		.371		0.443		.690
Yes	19/50 (38.0)		17/50 (34.0)		13/50 (26.0)	
No	55/121 (45.5)		34/121 (28.1)		28/121 (23.1)	
Nonretinal diagnosis		.140		0.034		.226
Yes	42/86 (48.8)		32/86 (37.2)		24/86 (27.9)	
No	32/85 (37.7)		19/85 (22.4)		17/85 (20.0)	
Uveitis		.126		0.236		.194 <sup>^</sup>
Yes	3/13 (23.1)		2/13 (15.4)		1/13 (7.7)	
No	71/158 (44.9)		49/158 (31.0)		20/158 (25.3)	

\*Broad therapeutic categories did not have a higher frequency of any type of artifact and are not included here.

<sup>†</sup> $\chi^2$  test used except for P value denoted with “<sup>^</sup>” where Fisher’s exact test was used.

IRM = Inner retina misidentification; ORM = outer retina misidentification.

univariable analysis were analyzed simultaneously with each other and with demographic variables. When these demographic and diagnostic variables were analyzed with stepwise selection, only variables that were significant were retained in the models. In this case, neovascular AMD was the only variable significantly associated with inner retinal misidentification. Three diagnoses, neovascular AMD, PVD, and non-AMD-associated choroidal neovascularization were significantly associated with outer retinal misidentification. Four diagnoses, neovascular AMD, macular hole, non-AMD-associated choroidal neovascularization, and ERM were significantly associated with the presence of any artifact. Both neovascular AMD and macular hole were significantly associated with inaccurate center thickness measurement.

## DISCUSSION

IN THIS REPORT, WE HAVE FOUND THAT OCT RETINAL scan artifacts are observed frequently, and, in many cases, they adversely affect the calculated retinal thickness measurement. Specific types of artifacts, including computer software misidentification of the inner and outer retina and “off center” artifacts, were most likely to produce inaccurate central retinal thickness measurements. These artifacts were often associated with particular ocular diseases and retinal therapy.

Certain types of retinal pathology or treatments were most apt to elicit specific types of scan artifacts. For example, eyes with neovascular AMD or choroidal neovascularization not associated with AMD, eyes with a macular hole, and eyes that had undergone photodynamic therapy, had inner and outer retinal misidentification artifacts. In these conditions, the disease (or treatment)

usually affects the integrity of the inner retina or RPE monolayer. For example, macular hole causes loss of both inner and outer retina, while choroidal neovascularization frequently disrupts the RPE. The OCT computer software requires clear delineation of the inner and outer retinal interfaces to accurately identify them. If it does not “see” a clear interface, an inner or retinal misidentification artifact will be produced. In eyes with macular hole, frequently the computer software “closed” the macular hole by connecting the line from one side of the hole’s inner retinal margin to the other, producing an inner retinal misidentification artifact. In eyes with choroidal neovascularization, the computer frequently did not properly identify the outer retina/RPE interface because the RPE was disrupted or obscured by the choroidal neovascular membrane. In this case, an outer retinal misidentification artifact was produced. In contrast, scans of normal eyes did not have inner and outer retina misidentification artifact and only had artifact related to user error. Interestingly, eyes with PVD had significantly increased outer retina misidentifications. The reason for this association is unknown. With currently available OCT software algorithms, these types of artifacts are unavoidable. Perhaps, with better recognition of particular artifacts that occur in association with specific retinal diseases, it will be possible to enhance the OCT software algorithms to minimize these types of artifacts.

In the present study, OCT scans were obtained very frequently to identify and manage macular edema caused by a variety of conditions. Nonetheless, artifacts were not observed significantly more frequently in eyes with macular edema than in those without. In eyes with macular edema not associated with choroidal neovascularization, the inner and outer retina is usually clearly delineated. Thus, inner and outer retinal misidentification errors, the most commonly observed artifacts in our study, are less likely to

**TABLE 2.** Univariable Analysis\* of Diagnosis and Any Artifact on FMTM Radial Scans

Diagnosis/Treatment	Number (%) With Artifact	P Value <sup>†</sup>
Neovascular AMD <sup>‡</sup>		.002
Yes	19/27 (70.4)	
No	55/144 (38.2)	
Full-thickness macular hole		.022 <sup>^</sup>
Yes	7/8 (87.5)	
No	67/163 (41.1)	
Photodynamic therapy for CNV <sup>§</sup>		<.001
Yes	12/14 (85.7)	
No	62/157 (39.5)	

\*Only statistically significant results are included. The Appendix includes all diagnoses/treatments that were analyzed.

<sup>†</sup> $\chi^2$  test used except for P value denoted with “^” where Fisher’s exact test was used.

<sup>‡</sup>Age-related macular degeneration.

<sup>§</sup>Choroidal Neovascularization.

occur. Other authors have demonstrated that macular thickness measurements can be reliably and reproducibly determined in eyes with diabetic macular edema.<sup>13</sup> We hypothesize that the lack of frequent inner and outer misidentification artifacts in eyes with diabetic retinopathy helps to explain the ability to obtain accurate retinal thickness measurements in this condition.

We observed inner retinal misidentification artifacts in eyes with vitreoretinal traction (in which the computer mistakes the vitreous membrane for inner retina) and outer retinal misidentification artifacts in eyes with subretinal fluid associated with macular edema (in which the computer mistakes the RPE for the outer retinal interface). However, these diagnoses were not significantly associated with inner retinal and outer retinal artifacts, respectively. These conditions were uncommon in our series. We speculate that vitreoretinal traction and subretinal fluid would have been significantly associated with inner and outer misidentification artifacts if a greater number of patients with these conditions had been studied.

Degraded image artifacts were observed frequently but were not associated significantly with cataracts. Although there may have been a physician selection bias to avoid OCT scans in eyes with the most severe cataracts, OCT was performed in a relatively high proportion of cataractous eyes. The ability to produce artifact-free OCT images in these cases points to the usefulness of OCT, even in eyes with moderately opacified ocular media.<sup>14,15</sup>

“Off center” artifacts were observed infrequently. These artifacts, however, could only be identified definitively when the foveal center could be seen on the surface map. In many cases, the foveal center could not be clearly identified on the surface map because of underlying pa-

**TABLE 3.** Univariable Analysis\* of Diagnosis and Inner Retina Misidentification (IRM) on FMTM Radial Scans

Diagnosis/Treatment	Number (%) With IRM	P Value <sup>†</sup>
Neovascular AMD <sup>‡</sup>		.023
Yes	13/27 (48.2)	
No	38/144 (26.4)	
Full-thickness macular hole		.052 <sup>^</sup>
Yes	5/8 (62.5)	
No	46/163 (28.2)	
Photodynamic therapy for CNV <sup>§</sup>		.006
Yes	9/14 (64.3)	
No	42/157 (26.8)	

\*Only statistically significant results are included. The Appendix includes all diagnoses/treatments that were analyzed.

<sup>†</sup> $\chi^2$  test used except for P value denoted with “^” where Fisher’s exact test was used.

<sup>‡</sup>Age-related macular degeneration.

<sup>§</sup>Choroidal Neovascularization.

thology. The photographers made every effort to center the fovea using the infrared camera. However, if a foveal depression was not present, it was not always possible to determine with absolute certainty whether the fovea had been properly centered. Because of this uncertainty, it is possible that the number of maps with “off center” artifacts was underestimated in this study. When “off center” artifacts were identified, they were sometimes associated with operator error, especially when underlying macular pathology was not present. They were also observed in eyes with macular disease, particularly neovascular AMD. In these cases, the patient may not have been able to fixate well on the target during the OCT scan. In these instances, it is especially important for the OCT operator to monitor through an infrared camera the patient’s fixation, and the position of the scan lines relative to the foveal center, during the scanning procedure. Even in eyes with neovascular AMD, a well-centered scan could usually still be obtained, even if it required a repeat scan (also see below), by careful operator attention to the foveal location during the scanning procedure. Development of better infrared camera optics might help the operator obtain a well-centered scan.

Certain types of artifacts were produced by the computer software and not necessarily related to the OCT operator. These included misidentification of the inner and outer retina and “out of register” artifacts. Others, including “cut edge” artifacts, and some “off center” artifacts, both of which occurred relatively infrequently, could be ascribed to user error. Often, if the scanning procedure was repeated, an artifact-free scan was obtained. If it was not possible to eliminate the artifact-containing radial scan by repeating the scanning procedure, the offending radial scan was frequently deleted to allow the computer to better

**TABLE 4.** Univariable Analysis\* of Diagnosis and Outer Retina Misidentification (ORM) on FMTM Radial Scans

Diagnosis/Treatment	Number (%) With ORM	P Value†
Neovascular AMD‡		<.001
Yes	14/27 (51.9)	
No	27/144 (18.8)	
Posterior vitreous separation		.053
Yes	11/29 (37.9)	
No	30/142 (21.1)	
Choroidal neovascularization		.007^
Yes	6/9 (66.7)	
No	35/162 (21.6)	
Photodynamic therapy for CNV§		<.001^
Yes	10/14 (71.4)	
No	31/157 (19.8)	

\*Only statistically significant results are included. The Appendix includes all diagnoses/treatments that were analyzed.

† $\chi^2$  test used except for P value denoted with “^” where Fisher’s exact test was used.

‡Age-related macular degeneration.

§Choroidal Neovascularization.

calculate central retinal thickness. In these instances, although the central thickness measurement was determined from fewer points, the thickness measurements were more accurate than if the thickness was determined from radial scans that contained artifacts that involved central fixation. It should be noted that “cut edge” artifacts can occur without having much effect on the surface map. In most of these scans the inner and outer retina lines continue to the edge of the scan as a close approximation to the true inner and outer retinal interface.

In most cases, OCT scan artifacts caused a false representation of the retinal surface map, but did not affect the cross-sectional scan image. For example, the cross-sectional scan would be valid even if the computer misidentified the inner or outer retina, and the clinician could use this valuable cross-sectional morphologic information to help assist with diagnostic and therapeutic decisions. Increasingly, however, clinicians have relied on quantitative information to evaluate the effect of particular therapies. In the case of neovascular AMD, retinal thickness correlates with visual acuity,<sup>16</sup> and it may be desirable to obtain an accurate central retinal thickness measurement upon which to base treatment decisions, even when it is not possible to obtain inner or outer-retinal misidentification artifact-free scans. Furthermore, retinal thickness is an important parameter that has been monitored in certain multicenter trials of drug therapy for neovascular AMD. In these instances, it would be more appropriate to measure retinal thickness on the scan printout manually (for example, with calipers) than to rely on the retinal thickness measurement determined by the computer.

**TABLE 5.** Univariable analysis\* of diagnosis and degraded image artifact on FMTM radial scans

Diagnosis/Treatment	Number (%) With Artifact	P Value†
Non-retinal diagnosis		.019
Yes	15/86 (17.4)	
No	5/85 (5.9)	
Pseudophakia		.323^
Yes	5/27 (18.5)	
No	15/144 (10.4)	
Cataract		.160
Yes	8/46 (17.4)	
No	12/125 (9.6)	

\*Only statistically significant and select results are included. The Appendix includes all diagnoses/treatments that were analyzed.

† $\chi^2$  test used except for P value denoted with “^” where a Fisher’s exact test was used.

Optical coherence tomography scan artifacts that caused an inaccurate central thickness measurement were seen frequently. In our study, when an artifact was identified by the OCT operator, many times the scan was repeated before the final image was placed in the patient’s medical record. The OCT operators who performed the scans in the present study were experienced, collectively scanning 3833 patients in 2002 and 5803 patients in 2003. It is likely that for inexperienced OCT operators, scan artifacts might go unrecognized even more frequently, producing an even greater number of inaccurate central retinal thickness measurements.

In some cases, retinal scan artifacts were present but did not affect the measurement of central retinal thickness. For example, we identified “cut edge” artifacts, or, occasionally, certain inner and outer retinal misidentification artifacts that occurred well away from the foveal center that would not affect the central retinal thickness measurement. Other artifacts, for example, “off center” artifacts, always affected the central retinal thickness measurement. Often, “cut edge” artifacts and “off center” artifacts are operator-induced and can be eliminated by careful attention to the scanning procedure. In our study, these types of artifacts were relatively infrequent, probably reflecting the extensive experience of the OCT operators. In an individual practice, if a high proportion of potentially avoidable scan artifacts are observed by the clinician, regardless of whether they affect the central retinal thickness measurement, then there may be a need for the OCT operator to obtain additional training to better identify scan artifacts and to learn methods to avoid them.

There are limitations to the current study. Four different operators performed OCT scans, and there may have been slight OCT scan technique variation from operator to oper-

**TABLE 6.** *P* Values From Multivariable Logistic Regression Modeling to Assess Simultaneous Effect of Broad Diagnostic and Therapeutic Categories Versus Artifact

Predictors	IRM*	ORM†	Degraded Image	Any Artifact	Inaccurate Center Thickness
Sex	0.673	0.203	0.428	0.528	0.800
Age	0.491	0.525	0.711	0.170	0.427
Macular diagnosis	0.090	0.040	0.891	0.270	0.046
Nonmacular retinal diagnosis	0.563	0.758	0.732	0.500	0.983
Nonretinal diagnosis	0.066	0.275	0.029	0.111	0.031
Macular therapy	0.706	0.500	0.737	0.193	0.073
Nonmacular retinal therapy	0.576	0.254	0.234	0.897	0.715

\*Inner retina misidentification.

†Outer retina misidentification.

ator. Optical coherence tomography scanning was performed by experienced operators, and the artifact frequency may not reflect that obtained by operators with different scanning experience. Furthermore, it is possible that some artifacts may not have been identified, causing an artificially low estimate of the frequency of scan artifacts. Some diagnostic groups were relatively small. Therefore, in instances where there was not a significant association between a scan artifact and a particular diagnosis, there may have been an inadequate sample size to identify a true association, if one existed. Regardless, the study reflects a “real-life” determination of OCT scan artifacts in a heterogeneous population of patients with vitreoretinal disorders. We believe that the primary study findings, a high rate of specific scan artifacts associated

with particular retinal diagnoses that can influence the central retinal thickness measurement, remains valid.

In summary, we have shown that OCT scan artifacts occur frequently and particular types of artifacts can be anticipated with the clinical retinal diagnosis. In many cases, scan artifacts are avoidable with particular attention to scan technique. In other instances, when artifacts cannot be avoided, their recognition can prevent inaccurate measurement of central retinal thickness. By understanding the types of OCT scan artifacts produced and the particular diagnoses that produce them, the clinician can minimize diagnostic and therapeutic errors when using this powerful imaging technique.

**TABLE 7.** *P* Values From Multivariable Logistic Regression Modeling With Stepwise Selection of Variables for Diagnoses and Demographic Information

Predictors	IRM*	ORM†	Degraded Image	Any Artifact	Inaccurate Center Thickness
Sex	—‡	—	—	—	—
Age	—	—	—	—	—
Race	—	—	—	—	—
Neovascular AMD§	0.026	<0.001	—	0.001	0.011
Posterior vitreous detachment	—	0.017	—	—	—
Macular hole	—	—	—	0.027	0.009
CNV¶	—	<0.001	—	0.034	—
Epiretinal membrane	—	—	—	0.016	—

Data shown as *P* values.

\*Inner retina misidentification.

†Outer retina misidentification.

‡Model did not come up with values.

§Age-related macular edema.

¶Choroidal neovascularization (non-AMD associated).

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## APPENDIX

### • DIAGNOSES AND INTERVENTIONS ANALYZED

#### *Retinal Diagnoses*

- Nonneovascular age-related macular degeneration
- Neovascular age-related macular degeneration
- Macular hole
- Vitreomacular traction
- Lamellar hole
- Epiretinal membrane
- Pigment epithelial detachment
- Retinal detachment
- Proliferative vitreoretinopathy
- Choroidal neovascularization
- Macular edema
- Nonproliferative diabetic retinopathy with and without macular edema
- Proliferative diabetic retinopathy with and without macular edema

- Subretinal fluid
- Subretinal hemorrhage
- Intraretinal hemorrhage
- Retinitis pigmentosa
- Presumed ocular histoplasmosis syndrome
- Subfoveal cyst
- Foveal cyst
- Central serous retinopathy
- Macular telangiectasia
- Subretinal scar
- Adult-onset foveomacular pigment epithelial dystrophy
- Metastatic lesion
- Angioid streaks
- Subretinal fibrosis
- Choroidal rupture
- Retinal neovascularization
- Posterior vitreous detachment
- Vitreous hemorrhage
- Retinal hemangioma
- Branch retinal vein occlusion with and without macular edema
- Hemiretinal vein occlusion with and without macular edema
- Central retinal vein occlusion with and without macular edema
- Cilioretinal artery occlusion
- Uveitis

#### *Nonretinal Diagnoses*

- Cataracts
- Aphakic
- Pseudophakia
- Increased intraocular pressure
- Corneal scarring

#### *Retinal Therapy*

- Full macular translocation
- Photodynamic therapy
- Focal photocoagulation
- Subretinal TPA
- Surgical repair for macular hole
- Intravitreal Kenalog injection
- Scleral buckle
- Retinal reattachment
- Pars plana vitrectomy
- Cryopexy

#### *Nonretinal Therapy*

- Cataract surgery

## CHAPTER 10

### DATA ANALYSIS, STATISTICAL ISSUES, AND DATA MONITORING

#### 10.1. STUDY DESIGN CHARACTERISTICS AFFECTING DATA ANALYSIS AND STATISTICAL ISSUES

The CATT: Lucentis-Avastin Trial is a prospective, randomized, non-inferiority clinical trial involving four treatment arms. The design of the trial is summarized in Chapter 2. Key aspects of the design and rationale that have major bearing on the approach to data analysis, statistical issues, and data monitoring are noted below:

- There are 4 treatment arms. Lucentis® on a fixed schedule of injections every month has the best demonstrated treatment efficacy at the beginning of the trial. Lucentis® on a variable schedule, Avastin® on a variable schedule and Avastin® on a fixed schedule are alternative approaches that would be preferred to Lucentis® on a fixed schedule if their treatment efficacy was as good as or better than (“non-inferior” to) the efficacy of fixed schedule Lucentis®. Given non-inferior efficacy, Lucentis® on a variable dosing schedule would be preferred to fixed schedule Lucentis®, and Avastin® on a variable dosing schedule would be preferred to fixed schedule Avastin®, because patients would have fewer injections, decreasing cost and decreasing risk of injection-related side effects. Avastin® on a variable dosing schedule or on fixed schedule would be preferred to Lucentis® on a variable schedule or on a fixed schedule if treatment efficacy were not inferior because Avastin® is much less expensive than Lucentis® on a per injection basis.
- At 12 months, the patients in the Lucentis® on fixed schedule arm will be randomized to continue with Lucentis® on fixed schedule or to Lucentis® on a variable dosing schedule for the next 12 months. Similarly, at 12 months, the patients in the Avastin® on fixed schedule arm will be randomized to continue with Avastin® on fixed schedule or to Avastin® a variable dosing schedule for the next 12 months.
- The primary outcome measure is mean change in visual acuity (VA) between the Initial Visit and the visit 12 months later (FV52).
- Secondary outcome measures at 1 year and 2 years are
  - Number of treatments
  - Percentage of eyes with a decrease in visual acuity of 3 lines or more (15 letters or more on the E-ETDRS chart)
  - Change in subretinal and intraretinal fluid on optical coherence tomography (OCT)
  - Change in lesion size on fluorescein angiography (FA)
  - Incidence of potential side effects of endophthalmitis, retinal detachment, cataract and uveitis
  - Incidence of systemic side effects
  - Cost

- The unit of randomization is eye. Only one eye of a person can be enrolled.
- Although the primary outcome is assessed at 12 months, longer term outcomes of treatment are of great interest because of the continued risk of loss of vision beyond 12 months.
- A subset of patients will have the grading of FAs and OCTs more frequently than other patients to allow analysis of the interplay of information from visual acuity, OCTs and FAs in predicting changes in visual acuity.

## 10.2. NON-INFERIORITY TRIAL DESIGN

### 10.2.1. Statistical modeling of the CATT: Lucentis-Avastin Trial design

The CATT: Lucentis-Avastin Trial is, in statistical terms, a non-inferiority trial among four active treatment arms; i.e., there is no placebo or untreated comparison arm. Non-inferiority trials are different conceptually from more familiar superiority trials and their design and analysis must be considered carefully (Garrett, 2003; Musch, 2006; European Medicines Agency, 2005; European Agency for the Evaluation of Medicinal Products, 2000). In the CATT: Lucentis-Avastin Trial, the Lucentis® on fixed schedule group is considered the reference group to which each of the two variable schedule arms and Avastin® on fixed schedule arm will be compared. The comparison of variable schedule Avastin® to variable schedule Lucentis®, variable schedule Avastin® to fixed schedule Avastin®, and fixed schedule Avastin® to variable schedule Lucentis® are also of interest. In terms of classic hypothesis testing, the six sets of hypotheses involved in the four-armed study are:

$$\begin{array}{lll}
 H_0: \mu_{LV} - \mu_{LF} \leq -\delta & \text{and} & H_A: \mu_{LV} - \mu_{LF} > -\delta \\
 H_0: \mu_{AV} - \mu_{LF} \leq -\delta & \text{and} & H_A: \mu_{AV} - \mu_{LF} > -\delta \\
 H_0: \mu_{AF} - \mu_{LF} \leq -\delta & \text{and} & H_A: \mu_{AF} - \mu_{LF} > -\delta \\
 \\ 
 H_0: \mu_{AV} - \mu_{LV} \leq -\delta & \text{and} & H_A: \mu_{AV} - \mu_{LV} > -\delta \\
 H_0: \mu_{AV} - \mu_{AF} \leq -\delta & \text{and} & H_A: \mu_{AV} - \mu_{AF} > -\delta \\
 H_0: \mu_{AF} - \mu_{LV} \leq -\delta & \text{and} & H_A: \mu_{AF} - \mu_{LV} > -\delta
 \end{array}$$

where  $\mu_i$  = is the mean change in visual acuity between initial visit and FV52 in group i,  
 $\delta$  = the maximum clinically acceptable true difference for treatments to be considered non-inferior, the “non-inferiority margin”,  $\delta > 0$   
LV denotes treatment with Lucentis® on variable schedule,  
LF denotes treatment with Lucentis® on fixed schedule,  
AV denotes treatment with Avastin® on variable schedule,  
AF denotes treatment with Avastin® on fixed schedule,  
and change in visual acuity is defined as the FV52 score minus the initial visit score (i.e., positive change means improvement).

**In non-inferiority trials, if  $\alpha$  is the significance level used for hypothesis testing, then observed treatment group differences that are associated with rejecting the null hypothesis are the same as those that fall below the lower limit of the  $(1-2\alpha)$  confidence interval.** (European Agency for the Evaluation of Medicinal Products, 2000). Thus, hypothesis testing at the 0.025 level corresponds to setting 95% confidence intervals. This choice allows easy and

valid switching of the interpretation of a non-inferiority trial to the interpretation of a superiority trial if the new treatment results in a better mean change than the referent treatment. Using confidence intervals is promoted as the best way to interpret trial results.

### 10.2.2. Special issues in non-inferiority trials

The FDA sets forth in section 1.5 of “Guidance for industry. E 10. Choice of control group and related issues in clinical trials” four major criteria for making valid conclusions from non-inferiority trials. (FDA, 2001). These criteria are listed below with comments on their application to the CATT: Lucentis-Avastin Trial.

1. *Historical evidence of sensitivity to drug effects*; i.e.; there is strong evidence that the reference treatment is efficacious.

Results released by Genentech on the results of their Phase III clinical trials provide strong evidence of a large treatment effect for Lucentis® on fixed schedule. Specifically, in the MARINA trial of fixed schedule Lucentis® versus sham treatment, 95% versus 62% of eyes with occult and minimally classic choroidal neovascularization lost less than 3 lines of visual acuity (15 letters) at 12 months. (Genentech press release, July 18, 2005). In the ANCHOR trial of fixed schedule Lucentis® versus photodynamic therapy with verteporfin (PDT), 94% and 95% (2 doses of Lucentis® ) versus 64% of eyes with predominantly classic choroidal neovascularization lost less than 3 lines of visual acuity. (Genentech Press Release Nov 7, 2005). Thus, fixed schedule Lucentis® has been shown superior to both sham treatment and to an approved active treatment (PDT).

2. *The design of the trial should be similar to the design of the trials used to establish that the drug is efficacious.* Design features such as study population, concomitant therapy, and outcome measures should be similar.

The CATT: Lucentis-Avastin Trial and the ANCHOR and MARINA trials have similar eligibility criteria, use change from baseline ETDRS visual acuity after protocol refraction as the primary outcome measure, and similarly restrict use of concomitant therapy for choroidal neovascularization.

3. *The trial conduct should be similar to the trials used to establish that the drug is efficacious and is of high quality.*

The CATT: Lucentis-Avastin Trial and the ANCHOR and MARINA trials share many of the same clinical centers. Fixed schedule Lucentis® in the CATT: Lucentis-Avastin Trial is administered with one of the 2 efficacious doses, at the same time intervals, without regard to OCT or angiographic findings. CATT has a full program of certification and quality assurance to ensure a high quality trial (adherence to study protocol, high follow-up rate, etc). In both the previous studies and the CATT: Lucentis-Avastin Trial, the primary analysis is an intention to treat analysis.

4. *An acceptable non-inferiority margin exists (non-zero) and takes into account historical data on efficacy and relevant clinical and statistical considerations.* The non-inferiority margin must be smaller than the believed smallest effect of the reference treatment.

Ophthalmologists are willing to accept a small, non-zero decrement in efficacy in return for fewer injections, substantially lower costs, and decreased risk of endophthalmitis and other injection-related adverse effects.

Factors leading to treatment group differences that are artificially small are of particular concern in non-inferiority trials, as reflected in criteria 2 and 3 above. Administering the reference drug in a manner different than that used to establish efficacy (thereby possibly decreasing efficacy), including patients with characteristics that disqualified participation in the earlier trials, and treatment group crossovers are some of the factors that can produce results that lead to the conclusion that two drugs are equally efficacious.

### **10.3. CHOICE OF PRIMARY OUTCOME**

The primary outcome measure for each treatment group is the mean change in visual acuity between initial visit and 52 weeks. Visual acuity, as measured with the E-ETDRS or ETDRS testing protocol, may be considered an interval scaled (Log MAR scale), continuous variable taking on values ranging from -82 to +77 (based on the eligibility criteria for the CATT: Lucentis-Avastin Trial). The mean is a precise summary measure for assessing whether one treatment has shifted the distribution of visual acuity towards improvement more than an alternative treatment.

Until the advent of Lucentis®, the vast majority of eyes with newly diagnosed subfoveal choroidal neovascularization lost vision over the next 1 to 3 years; only a small percentage of patients had improved vision over time. The distributions of change in visual acuity were fairly well characterized by the percentages in specified tail areas (e.g., 15 letter loss or 30 letter loss corresponding to 3 and 6 line loss of a doubling or quadrupling, respectively of the minimum angle of resolution). In addition, such losses have a clinically significant impact on the patient's function. However, the results from the MARINA and ANCHOR trials show that with fixed schedule Lucentis®, visual acuity can improve substantially (several lines) and that there is little room to show improvements in treatment efficacy by decreasing the 5% of eyes suffering a 3-line loss (15 letters) with treatment.

Given the underlying continuous measurement scale, the high likelihood for both increases and decreases in visual acuity score, and the inability of the traditional 3-line loss dichotomy to accommodate measurement of further improvements in treatment efficacy, mean change is a strong choice for the primary outcome. The higher precision of a mean relative to a proportion is desirable in non-inferiority trials where the interpretation is driven by the width of the confidence interval. The only major drawback to the choice of using mean change is the absence of description of differences in clinically meaningful changes in the distribution. However, this shortcoming can be overcome by secondary outcome measures and through the use of descriptive statistics.

### **10.4. SAMPLE SIZE CONSIDERATIONS**

#### **10.4.1. Approach to Sample Size**

A non-inferiority trial approach to sample size and power calculations is used for the main treatment group comparisons in the CATT: Lucentis-Avastin Trial. The sample size for

comparisons between groups created by the second randomization at 52 weeks for patients in the initial fixed arms of Lucentis® and Avastin® is based on a non-inferiority approach. The calculations for the substudy on fluorescein angiography and OCT are based on achieving high power for detecting dichotomized risk factors.

#### 10.4.2. Assumptions for the Sample Size Calculations for the CATT: Lucentis-Avastin Trial – Primary Analysis

Several assumptions must be made in order to calculate sample size:

- Overall Type I ( $\alpha$ ) error rate of 0.025 (see 10.2.1 above)
- Bonferroni adjustment for 6 primary comparisons yields an adjusted  $\alpha$  error rate of 0.025/6 or 0.0042.
- Statistical power of 90%.
- The standard deviation of the distribution of changes ( $\sigma$ ) in visual acuity is 15 letters (3 lines). This assumption is based on the observed standard deviations in recent trials of treatments for choroidal neovascularization. At 1 year, the published standard deviation in the verteporfin group in the VIP study for occult or minimally classic lesions was 13.4 letters. (VIP Therapy Study Group, 2001). Other studies have not published standard deviations of the treated group; however, back calculations based on knowing the mean change, the percentages with 15 letters lost or gained, and the percentile distribution of the normal (Gaussian) distribution provides additional estimates. (Genentech press release, July 18, 2005) In Genentech's MARINA trial, the mean change in both the Lucentis® dose groups was 7 letters improvement and 5% lost 15 or more letters. In the 0.3mg dose group, 25% of patients had a gain of 15 letters or more, in the 0.5mg group, 34% had a gain of 15 or more letters. These three percentages from the same group of patients yield estimates of  $\sigma$  of 13.4, 11.9, and 19.4 letters, respectively. In Alcon's Phase III of anecortave acetate versus PDT for eyes with predominantly classic lesions, the difference between treatment groups in mean change at 12 months was 0.06 Log MAR, or 3 letters, with a p-value of 0.03. Back calculating from the p-value with a t-distribution, yields an estimate of  $\sigma = 16$  letters from the pooled estimate of variance. Based on the 5 estimates (11.9, 13.4, 13.4, 16, and 19.4) an estimate of 14 or 15 is reasonable.
- The maximum clinically acceptable true difference for new treatments to be considered non-inferior,  $\delta_L$  or the "non-inferiority margin", is 5 letters (just 1 line on the visual acuity chart). Factors considered in choosing this important value include:
  - Ophthalmologists and patients are reluctant to sacrifice visual acuity to gain the benefit of large cost savings and decreased number of injections.
  - The observed difference in mean change in visual acuity at 52 weeks between fixed schedule Lucentis® and sham treatment was 17 letters (3.4 lines) in the MARINA study. A  $\delta_L$  of 5 letters would be approximately 29% of the estimated treatment effect from the MARINA study.

- Historically, treatments for neovascular AMD with a difference in mean change in visual acuity of 1.2 to 1.4 lines (6 to 7 letters) between active treatment and placebo/sham control have been accepted as sufficiently efficacious to be used in clinical practice and/or approved by the FDA. The non-inferiority margin should be smaller than the difference that separates an efficacious treatment from no treatment. Therefore,  $\delta_L$  for the CATT: Lucentis-Avastin Trial should be less than 1.2 lines (6 letters).

Trial/Treatment	Time	Mean Change (VA Lines)		Difference	Percent with 3-line loss
		Drug	Control		Difference
MPS / Laser <sup>1</sup>	24 mo	-3.0	-4.4	1.4	20%
TAP/PDT <sup>2</sup>	12 mo	-2.2	-3.5	1.3	15%
TAP/PDT <sup>2</sup>	24 mo	-2.7	-3.9	1.2	15%
VIP/PDT <sup>3</sup>	24 mo	-3.8	-5.1	1.3	12%
Eye001/Macugen <sup>4</sup>	12 mo	-1.6	-3.0	1.4	15%

<sup>1</sup> Macular Photocoagulation Study Group, 1991

<sup>2</sup> TAP Study Group, 1999

<sup>3</sup> VIP Therapy Study Group, 2001

<sup>4</sup> Gragoudas, 2004

- The anticipated true difference between treatment groups ( $\delta_1$ ) is 0. That is, both treatment arms are expected to have the same efficacy.
- The statistical test used to compare the two treatment groups at 12 months is an independent t-test on the mean change in visual acuity from the initial visit.
- The percentage of patients completing visit FV52 is 95%. Patient death, illness, and re-location may result in incomplete data. This assumption is reasonable given the 94% completion rate in the TAP PDT trial (TAP Study Group, 1999) and the 98% completion rate in the Complications of AMD Prevention Study.

#### 10.4.3. Sample Size and Power Calculations – CATT: Lucentis-Avastin Trial

The sample size is calculated by using the above assumptions and the sample size formula for comparing two means in a non-inferiority trial as implemented in the statistical software program PASS 2005 (Number Cruncher Statistical System, Kaysville, Utah). The total number of patients required for analysis in each treatment group is 277, or 1108 total for the entire study. If approximately 8% do not complete the examination at 52 weeks, 300 patients in each group (1200 total) will need to be recruited.

Additional calculations in the table below show that the sample size of 277 patients in each arm for analysis will provide high statistical power to reject non-inferiority under a number of reasonable alternative value of  $\sigma$  and alternative number of multiple comparisons.

### Sample Size Needed for Analysis for Each of 4 Treatment Groups

Number of comparisons	$\alpha$	$\sigma$	Power	
			80%	90%
2	0.0125	14	150	195
6	0.00417	14	191	242
2	0.0125	15	172	224
6	0.00417	15	219	277
2	0.0125	16	195	255
6	0.00417	16	249	316

#### 10.4.4. Sample Size and Power Calculations – OCT and FA Substudy

All patients will have their FAs and OCTs from baseline, 52 weeks and 104 weeks graded and analyzed for the purposes of outcome assessments. A subset of patients in the CATT: Lucentis-Avastin Trial will be chosen from among the first patients enrolled to have grading and analysis of additional FAs and OCTs as part of the OCT and FA Substudy. These patients also will have the FAs taken at 12, 24 and 80 weeks and the OCTs taken at 4, 8, 12, 24, and 80 weeks graded and analyzed. To better understand the relation between OCT and FA before and during treatment with anti-VEGF agents, correlations will be examined among OCT characteristics and FA characteristics at each time angiograms are taken. In addition, FA and OCT characteristics before and after the initial treatment will be explored for their prognostic value for visual acuity at 52 and 104 weeks. Patients from all four patient arms will be pooled because the relations among OCT, FA, and visual acuity are not expected to vary between Lucentis® and Avastin®.

Only 300 patients will have the additional gradings of FAs and OCTs. Because the proposed analysis is exploratory in nature, the precise analysis on which to base sample size calculations cannot be specified. The power to detect prognostic factors from among the FA characteristics from these additional time points will depend on the proportion of patients with the candidate risk factor (e.g., proportion with FA leakage at 8 weeks), the risk of the defined indicator of poor visual acuity outcome (e.g., visual acuity at 52 weeks worse than at initial visit), and the strength of the risk factor (relative risk). The table below shows that for a wide range of scenarios, 300 patients provides high statistical power (80% or better **highlighted**) of identifying ( $\alpha=0.05$ ) a clinically important prognostic factor (relative risk above 1.5). During analysis, efforts will be made to define poor VA outcome measures that are present in approximately a third of the patients (such as the worst tertile). Power calculations were performed using the statistical software program PS (version 2.1.31; Dupont, 1990).



Proportion with risk factor	Risk of poor VA outcome in those without factor	Relative Risk		
		2.00	1.75	1.5
50%	50%	1.00	1.00	0.99
	30%	1.00	0.98	0.77
	15%	0.88	0.67	0.38
25%	50%	1.00	1.00	0.98
	30%	1.00	0.94	0.66
	15%	0.80	0.59	0.34
15%	50%	1.00	1.00	0.90
	30%	0.97	0.83	0.51
	15%	0.66	0.47	0.27

With four times the number of patients available for analyses involving OCT scans and/or the annual FAs, there will be high power for detecting much lower relative risks.

#### 10.4.5. Precision of the Estimate of the Difference in Change in Visual Acuity in each of the Two Groups Initially Assigned to Fixed Schedule of Lucentis® and Avastin®

After randomization at 52 weeks to either continuation of fixed schedule or on variable schedule for both Lucentis® and Avastin®, there will be approximately 143 patients in each of these subgroups (95% completion rate at 52 weeks). At 104 weeks, if the standard deviation of change in visual acuity remains at 15, the 95% confidence interval will be approximately (mean difference)  $\pm 1.96 \sqrt{(2/143)} * \sigma$ , or (mean difference)  $\pm 3.5$  letters.

### 10.5. DATA ANALYSIS

#### 10.5.1. Statistical Methods to be Applied

Data analysis will be conducted using standard statistical techniques for comparing two independent groups: chi-squared tests for equality of proportions, independent t-test for equality of means, Wilcoxon rank sum test, multiple logistic and linear regression, and proportional hazards modeling. The distribution of continuous variables will be assessed by measures of normality and graphical displays so that non-parametric methods or data transformations may be applied when appropriate.

#### 10.5.2. Assessment of Baseline Comparability of Treatment Groups

Tables will be generated and inspected to compare, by treatment group, the distribution of key baseline variables having descriptive and prognostic importance. These variables will include, but not be limited to, patient age, race, ethnicity, gender, cigarette smoking status, hypertension, use of anti-oxidant vitamins, visual acuity, lesion size, lesion composition, presence of retinal angiomatous proliferation (RAP) features, retinal thickness, and presence of cysts on OCT.

### 10.5.3. Data Analyses of the Primary Outcome Variable

The primary statistical analyses will be performed on an intent-to-treat basis. There is some controversy about whether the “per protocol” study population should be used for the primary analysis in non-inferiority trials; however, recent examination of the question does not yield any clear benefit in using the “per protocol” subset of patients (Garrett, 2003). Furthermore, use of a per protocol study population may create problems if inferiority is rejected and a test for superiority is conducted because intention-to-treat study populations are generally preferred for superiority trials.

The primary outcome measure is the mean change in visual acuity (VA) at 52 weeks. The primary assessment of efficacy will be based on pairwise comparisons in mean change in VA between groups. If there are no imbalances on important prognostic factors at baseline, a simple independent t-test and corresponding confidence intervals will be used for evaluation of treatment differences. If there are imbalances in the key prognostic factors at baseline (baseline visual acuity score and lesion size) linear regression models will be used to estimate the difference in mean change in VA between treatment groups and the confidence intervals derived from the corresponding standard error of the estimate. These models will also include indicator variables for clinical center because the randomization is stratified by center. The Bonferroni adjustment will be used to accommodate the 6 main pairwise comparisons of interest (see section 10.2.1 above); therefore an  $\alpha$  level of 0.0042 will be used for hypothesis testing and confidence intervals will be  $(1-2\alpha)$  or 99.16% confidence intervals. If the null hypothesis of inferiority is rejected, testing for superiority will be performed. That is, if the lower confidence limit for the difference in mean VA change lies within  $(-5, \infty)$ , the null hypothesis of inferiority will be rejected and the non-inferiority will be established. Furthermore, if the lower confidence limit lies within  $(0, \infty)$ , superiority will be established (European Agency for the Evaluation of Medicinal Products, 2000).

Analyses will be performed to assess the robustness of the results with respect to dropouts and non-compliance with the eligibility criteria and the treatment protocol. In addition to the above-described analysis of results from all patients who complete the 52-week examination (completed cases) with their treatment group assignment classified as assigned at randomization (“intent-to-treat”), an intent-to-treat analysis will be performed using “last observation carried forward (LOCF)” for the visual acuity value of patients who do not complete the 52-week examination. Also, a “per protocol” analysis, including only those patients who met all eligibility criteria at baseline and whose assigned treatment was carried out as specified in the protocol, will be performed.

Additional analyses to more fully characterize the relation of mean visual acuity over time will be performed using longitudinal data analysis methods (Liang, 1986). Visual acuity scores from all visits with protocol refraction preceding measurement of visual acuity will be incorporated. Both the relation of visual acuity with follow-up time and the influence of possibly prognostic factors will be evaluated using these models. Subgroup analyses will be performed to assess the consistency of the treatment effect across clinics and the levels of important baseline covariates. To date, no effect modifiers have been identified for the anti-VEGF agents Macugen® and Lucentis® (Gragoudas, 2004; Genentech Press releases of July 18 and November 7, 2005). However, the role of specific OCT characteristics has not been fully explored and the decision on not prespecifying particular subgrouping factors as candidates for effect modification will be

reconsidered prior to the first data analyses of visual acuity data for the Data and Safety Monitoring Committee.

#### **10.5.4. Data Analyses of Secondary Outcome Variables**

Specific secondary outcome variables for the CATT: Lucentis-Avastin Trial are number of treatments, 3-line change in VA (15 letters on ETDRS chart), change in subretinal and intraretinal fluid on OCT, change in lesion size on fluorescein angiography, cost of treatment, and incidence of endophthalmitis, retinal detachment, cataract and uveitis. These secondary outcome measures are assessed at Year 1 and Year 2.

##### **10.5.4.1. Number of Treatments**

The number of treatments after initial treatment is an especially important secondary outcome measure because if either or both of the “on a variable schedule arms” is not found inferior to fixed schedule, then the major criterion for choosing treatment will be the number of injections required. This variable has a limited range (0-12 in the first year and 0-25 through the second year) and is likely to be highly skewed. The median number of treatments will be the primary summary measure and comparisons between the two “on a variable schedule arms” of the trial will be with the Wilcoxon rank sum test. In addition, Poisson regression will be used to compare groups and consider the influence of other factors.

##### **10.5.4.2. 3-line Change in Visual Acuity**

As noted above in 10.3, 3-line decrease (15-letter decrease, doubling of the minimum angle of resolution) in visual acuity have been used historically as a primary outcome variable. The proportion with 3-line increase and with 3-line decrease in each treatment group will be compared to supplement the statistical analysis of mean change in visual acuity. Results at 52 weeks and 104 weeks will be of particular importance.

##### **10.5.4.3. Change in Subretinal and Intraretinal Fluid**

Changes from initial visit in subretinal and intraretinal fluid will be assessed using both discrete and continuous variables. Presence and absence of fluid at 52 weeks and 104 weeks will be evaluated among treatment groups using chi-square tests of proportions supplemented with logistic regression. Change in retinal thickness at 52 and 104 weeks will be evaluated among groups using analysis of variance (ANOVA) and linear regression techniques. As for the primary outcome variable, longitudinal models will be used to more fully characterize the relation of these OCT characteristics over time and to identify factors other than treatment group that influence intraretinal and subretinal fluid.

##### **10.5.4.4. Change in Size of Lesion**

Changes from initial visit in size of lesion will be assessed using as a continuous variable (area of lesion on fluorescein angiography at 52 weeks and 104 weeks). Analysis of variance (ANOVA) and linear regression techniques will be used to compare changes in lesion size among the treatment groups. Longitudinal models will be used to more fully characterize the relation of lesion size over time and to identify factors other than treatment group that influence intraretinal and subretinal fluid.

#### **10.5.4.5. Cost**

The cost of delivery of each of the treatment arms through 1 and 2 years will be determined by using the observed number of treatments and the Medicare reimbursable rates for the study drug, injections, office visits, and diagnostic tests (OCT and photography) needed to deliver the treatment. The cost of treatment will be compared between treatment arms.

#### **10.5.4.6. Incidence of Adverse Events**

Systemic adverse events and ocular adverse events such as endophthalmitis, retinal detachment, cataract, and uveitis are expected at a very low rate in all of the treatment groups. Comparisons across treatment groups of these rates will be made using survival analysis techniques – Kaplan-Meier curves with differences assessed with the logrank test.

#### **10.5.5. Handling Missing Data**

Major efforts will be made by the entire CATT group to avoid loss to follow-up and subsequent missing data. However, despite these efforts some data for the primary and secondary outcome measures may be missing. The percentage of data missing for major analyses will be tabulated. The characteristics at baseline, and during follow-up, of patients who ultimately are unavailable for follow-up will be assessed by comparing distributions between those under follow-up to those who are lost to follow-up. When available, the reasons for loss to follow-up will be reviewed. If missing data from living patients account for more than a small percentage of expected data (>5%), key analyses will be performed not only with the actual observed data on patients under follow-up, but also, using multiple imputation methods (Rubin, 1987; Heyting, 1992; Lavori, 1995). Both predictive model based methods and propensity score methods will be used to evaluate the impact of missing data on the key analyses of the CATT. Multiple imputation methods have better statistical properties than alternatives such as complete case analyses or single imputation.

#### **10.5.6. Data Analyses for OCT and Fluorescein Angiography Substudy**

Analysis of the data from the OCT and fluorescein angiogram (FA) gradings of participants in the OCT and Fluorescein Angiography Substudy will focus on the relationships among OCT characteristics and FA characteristics at different points in follow-up time and on the time relationships between resolutions and reappearances of fluid on OCT and fluorescein leakage and subsequent visual acuity. These analyses will first be developed combining all treatment groups and will be examined to see if the relationships vary by treatment group (interaction).

Correlation between FA characteristics (change in lesion size, dye leakage, retinal angiomatous proliferation) and OCT characteristics may change over time. For example, after the initial treatments, persistent subretinal fluid on OCT may be associated with lesion growth on FA, but by 12 months of follow-up there may be no association between subretinal fluid and further lesion growth. Analyses aimed at clarifying the relationship between presence of fluid on OCT and leakage on FA will be performed.

Exploration of the prognostic role of FA and OCT will be done in several ways. In the text that follows, the analyses are described for leakage on FA, but an identical approach will be take for fluid and retinal thickness on OCT.

- Longitudinal models of visual acuity over time with the presence of leakage as a time dependent covariate, with exploration of time-lagged variables;
- Exploration of patterns over follow-up time of leakage and VA at 12 and 24 months; e.g. do eyes that have resolution leakage by 2 months with no reappearance have better VA at 12 months than eyes without such resolution or eyes with intermittent periods of leakage?
- Repeat of analyses described above with VA at 24 months as the outcome measure;
- Addition of other covariates that may be indicators of treatment efficacy to the models developed above, especially OCT characteristics, to estimate the incremental information gained from knowledge of fluorescein leakage.

### **10.5.7. 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. 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.

### **10.5.8. Software for Statistical Analysis**

SAS/STAT software (SAS Institute, Inc., 100 SAS Campus Dr., Cary, NC, 27513-2414) is used for performing most statistical analyses. SAS Procedures are available for the vast majority of analysis methods described above, including the multiple imputation methods. Additional software packages are resident on the computer system for the Coordinating Center to handle specialized applications, such as Confidence Interval Analysis (CIA) for Windows (University of Southampton School of Medicine ([www.medschool.soton.ac.uk/cia/](http://www.medschool.soton.ac.uk/cia/))). When the application can be accommodated more easily by other software packages, Stata (StataCorp, 4905 Lakeway

Drive, College Station, Texas 77845) and S-Plus (1700 Westlake Avenue North, Suite 500, Seattle, WA 98109-3044) are available.

## **10.6. DATA MONITORING**

The CATT Data and Safety Monitoring Committee (DSMC) will follow “NIH Policy For Data And Safety Monitoring” - release date: June 10, 1998) and the “National Eye Institute Guidelines for Data and Safety Monitoring of Clinical Trials” NOTICE: EY-01-002, release date March 2001. The NEI guidelines provide explicit guidelines on responsibilities of the Committee, membership, meeting format, recommendations, release of data, and conflict of interest which have been incorporated into CATT DSMC Charter and will not be repeated here in full. A few areas of particular importance to CATT will be noted below.

### **10.6.1. Initial Meeting**

In addition to the review of protocol required by NEI guidelines, during the first meeting of the Data and Safety Monitoring Committee, the biostatisticians in the Coordinating Center will provide the members with background on the statistical and practical aspects of decisions on treatment efficacy or safety before the scheduled end of the clinical trial (Wittes, 1993). The overall statistical analysis plan and the plan for safety monitoring will be reviewed.

The biostatisticians will recommend that statistical monitoring of the CATT: Lucentis-Avastin Trial, a non-inferiority trial, for early stopping be managed through the approach of repeated confidence intervals (Durrleman, 1990; Jennison, 1984). This method applies the sequential monitoring Z values that would be applied to interim hypothesis testing to the construction of confidence intervals at each interim analysis. The approach of O’Brien and Fleming for calculation of the Z values will be suggested for adoption by the Data and Safety Monitoring Committee.

### **10.6.2. Safety Monitoring**

The Medical Monitor, chosen by the study chair and NEI staff before subject enrollment begins, will bear special responsibility for review of adverse events. All serious adverse events reports will be transferred to the Medical Monitor upon receipt by the Coordinating Center as described in Chapter 6 on Adverse Events. The Medical Monitor will alert the study chair and the chair of the DSMC if there is a safety issue that warrants immediate discussion by teleconference.

The full DSMC will review all serious adverse events and tabulations of non-serious events during meetings held twice yearly. The chair of the DSMC must provide an annual report for submission to local Institutional Review Board (IRBs) that the Committee has reviewed the safety data with a recommendation for continuation or modification of the trial.

### **10.6.3. Stopping because of Safety**

There will be no formal statistical guidelines for stopping because of safety considerations. The magnitude of the difference in safety outcomes, as well as their severity, will be considered in deciding whether the trial should be stopped. In addition, review of efficacy may be necessary in order to weigh the negative effects of the drug relative to the positive effects. In general, the

strength of evidence that the study drug is unsafe does not need to be as strong as the strength of evidence needed to stop a trial because of beneficial treatment effects on efficacy.

#### **10.6.4. 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 11

### QUALITY ASSURANCE ACTIVITIES

#### 11.1 OVERVIEW

The Coordinating Center has primary responsibility for assuring that the quality of the data collected and reported in the study are of consistently high quality. Many factors contribute to the quality of the data, from the design and procedures of the trial to the analytic methods employed. The Coordinating Center works with the Fundus Photograph Reading Center and OCT Reading Center on the design and implementation of a quality assurance program for grading photographs and OCTs. Similarly, Coordinating Center staff work with the Drug Distribution Service to implement a quality assurance program for tracking study drug inventory.

#### 11.2 GENERAL QUALITY ASSURANCES

The major quality assurance features of the study are:

- Standard data collection forms and procedures;
- Common protocol for eligibility, examination, and follow-up of all patients in all clinical centers;
- Computerized treatment allocation with eligibility review preceding enrollment;
- **MASKED** assessment of the primary outcome measure and secondary outcome measures;
- Ophthalmologists **MASKED** to study drug when deciding on retreatment;
- Central masked grading of photographs and OCTs;
- Direct data entry into the study database at the Clinical Centers
- Central, computer driven data editing for missing, invalid, and suspect responses;
- Regular reporting on performance of all Clinical Centers;
- Monitoring visits to all centers;
- Specific data analyses to identify incorrect or fraudulent data collection processes;
- Certification of clinic staff and of imaging equipment;
- Regular meetings of the Investigative Group to review methods and discuss problems.

Staff at the Coordinating Center and Reading Centers participate in the design of all data collection forms, coordinate modifications to existing forms, and develop new forms as needed. Because the Coordinating Center supplies all centers with master copies of forms, it



ensures that the current versions of all forms and components are available to the clinical centers in the rare event that the on-line system is temporarily unavailable.

The members of the CATT Planning Committee played a major role in developing the Lucentis®-Avastin® Trial protocol and preparing the *Manual of Procedures*. Coordinating Center personnel and those from the Reading Centers update the chapters of the *Manual of Procedures* and are responsible for periodically distributing updates to all centers.

Biostatisticians and the Systems Analyst at the Coordinating Center prepare the treatment allocation schedules for each clinic. Treatment group allocations are issued only after verification of eligibility via the on-line database management system.

Coordinating Center staff members are responsible for ensuring that all data processing activities in the study proceed smoothly, as described in Chapter 16, and for timely editing, resolution of problems, and reporting. Concurrent data processing and editing are important for providing feedback to each individual involved in data collection and submission and to those involved in patient care to ensure that the procedures specified in the protocol are properly interpreted and applied.

Protocol Monitors of the Coordinating Center have primary responsibility for visiting the Clinical Centers to ensure protocol adherence and to assist in identifying and resolving problems. Other Coordinating Center staff also assist with these visits as necessary. Staff at the Coordinating Center provides information to the Director to facilitate the activities of overseeing clinical center operations.

Biostatisticians at the Coordinating Center develop 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 Director of the Coordinating Center is responsible for the certification program for the study (see Chapter 16). In addition to the initial training of Clinic Coordinators, the Director and Protocol Monitor also organize and chair sessions for the Clinic Coordinators at the annual meetings. Problems and issues related to following the protocol, handling of study medications and submission of data and images 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 component of quality assurance. These meetings provide a mechanism of sharing information among CATT investigators and other personnel. The Coordinating Center staff, with input from the Chairman's Office and Operations Committee, plays a major role in organizing these meetings and preparing reports and presentations to be made to the Investigative Group.

### **11.3 CLINICAL CENTER MONITORING COMMITTEE**

The Clinical Center Monitoring Committee has responsibility for the quality assurance activities required to maintain standardization of procedures and adherence to the CATT protocol. Membership and specific functions may be found in Section 12.11. Problems in Clinical Center performance or adherence to the protocol are normally resolved by the Director and Protocol Monitor working directly with the staff of the clinic. When these efforts fail, the problem is referred to the entire committee. If necessary, the Clinical Center Monitoring Committee reports failure to resolve the issue to the Operations Committee or the Executive Committee.

### **11.4 SITE VISITS TO CLINICAL CENTERS**

Periodic site visits by an independent observer are necessary to ensure 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. All sites will be visited within a few months of the initiation of patient recruitment and will then be performed every other year on a staggered schedule. Clinical Centers may be visited more frequently if the Clinic Monitoring Committee deems it necessary due to problematic performance or clinic staff turnover.

#### **11.4.1. 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 to the Clinic Coordinator. The site visitors re-arrange the agenda to meet the scheduling constraints of the clinical center.

Site visitors prepare for the visit by reviewing previous site visit reports, notes from recent triannual telephone calls, clinic report cards issued by the Clinical Center Monitoring Committee and any comments or concerns from the Fundus Photograph and OCT Reading Centers regarding the Clinical Center. The data processing staff prepares data to be checked against clinic forms and original source materials.

The Clinic Coordinator prepares by making sure that patients and staff are available for the site visitor to observe the Refractionist, Visual Acuity Examiner, Photographer, OCT technician and Clinic Coordinator perform the entire set of study protocols. The site visitors may ask the Clinic Coordinator to assist in making arrangements for local lodging and transportation.

#### **11.4.2. Conduct of the Visit**

Site visits will begin early in the morning and will generally require 1-2 days. 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 implement, the clinic personnel are instructed to follow the protocol. The site visitors bring the issue to the Operations Committee, Executive

Committee, Director of the Coordinating Center, Study Chairman 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
- Storage and access to study medications and drug accounting procedures
- Flow of patients through the clinic during study visits with special emphasis on procedures for OCT, photography and visual acuity testing
- Up-to-date study documentation including the *Manual of Procedures*, data collection form masters, protocol memoranda, study medication inventory and tracking documentation, documentation confirming reports of serious adverse events to the local IRB and other regulatory documents.
- Review of signed consent forms for 100% of patients during the enrollment period
- Review of a sample (approximately 5%) of data collection forms for comparison with data in the CATT database and source documents
- Observation of the Clinic Coordinator during at least one patient visit
- Observation of the Refractionist and Visual Acuity Examiner(s) performing the refraction or visual acuity testing, respectively, on a study patient.
- Storage and access to study patient files, including proper storage of signed consent forms and handling of edit messages
- Discussion of individual patients with follow-up problems
- Meeting with the Principal Investigator of the clinic to discuss recruitment, follow-up, and areas of concern

#### **11.4.3. Site Visit Reports**

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

#### **11.5 REGULARLY SCHEDULED TELEPHONE CALLS**

A telephone call is scheduled once every 4 months (unless a site visit has recently occurred) between the Protocol Monitor and clinic coordinator to ensure that changes (if any) in study 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, to the attention of the Protocol Monitor or Director.

## **11.6 PREVENTING DROP-OUTS AND MISSED VISITS**

Each Clinical Center must make visits as pleasant as possible by minimizing wait time, and providing comfortable waiting and examination facilities. The Coordinator and the PI for each Clinical Center will continually educate the patient as to the nature of the Study, the need for the patient's continued participation, and answer questions concerning AMD, CNV, medications used in the Study and if necessary, provide assistance with erroneous billing.

The Coordinator will contact patients to remind them of a follow up visit within the week of the appointment. The contact can be by telephone or email but a patient response is necessary. To ensure patient compliance for scheduled visits, early morning, evening or weekend hours may be provided. Every effort must be made by the Clinical Center to remain in contact with patients, even if they do not want to return to be examined or follow the protocol.

## **11.7 QUALITY ASSURANCE RELATED TO DRUG STORAGE AND ACCOUNTABILITY**

Vials of Avastin<sup>®</sup> will be supplied to each center by the Drug Distribution Service. Lucentis<sup>®</sup> will be purchased by the clinical center in a manner consistent with non-study patients. Each Clinical Center will store both drugs in a refrigerator in their local pharmacy or in locked areas at the Clinical Center in a manner consistent with their standard clinical practice. All refrigerators will have a temperature alarm to alert staff if the temperature deviates beyond the boundaries of 2°-8°C (36°-46°F). At the time of treatment with either study drug, the clinic coordinator will record the identifying vial information onto the drug inventory logs. The Drug Distribution Center provides a "CATT Medication Ordering, Distribution, and Accountability Manual" to each clinical center. Outdated supplies will be recalled by the Drug Distribution Center and replacement supplies provided.

All drug storage facilities and study treatment records will be made available to the site visitor for inspection during site visits.

## **11.8 ENSURING DATA INTEGRITY AND QUALITY**

Ensuring the integrity and quality of data collected in the CATT is critical. Refer to Section 16.5 for CATT Quality Assurance activities related to data management.

## CHAPTER 12

### ORGANIZATIONAL STRUCTURE OF THE STUDY

#### 12. ORGANIZATIONAL STRUCTURE OF THE STUDY GROUP

##### 12.1 Introduction

The functional units in the trial are the Chairman's Office, Coordinating Center, Fundus Photograph Reading Center, OCT Reading Center, the Drug Distribution Service, and Clinical Centers. The administrative organization consists of an Executive Committee, an Operations Committee, a Treatment Review Committee, a Clinic Monitoring Committee, a Data and Safety Monitoring Committee, the Investigative Group and other committees as required. See Exhibits 12-1 and 12-2 for a schematic of the organizational structures within the CATT.

##### 12.2 Chairman's Office

The Chairman's Office provides the scientific and medical guidance for directing all committees except the DSMC. The Chairman provides steady leadership for the overall performance of all aspects of the study. The Chair is assisted by the CATT Vice-Chair, especially in matters related to negotiating with outside organizations such as the Food and Drug Administration and the Centers for Medicare and Medicaid Services. (See Chapter 15 for more details on the role of the Chairman's Office.)

##### 12.2.1. Responsibilities

The Chair is responsible for overseeing the scientific direction of the Study, maintaining effective study committees, and keeping an operative working group of investigators. Specific responsibilities may change during the course of the study to meet changing needs. Responsibilities will include, but not be limited to, the following:

- Monitoring of study progress. During the study, monthly documentation on recruitment at each clinic is used by the Chair to encourage and assist each site to reach recruitment goals. The Chair also monitors the most prolific recruiting clinics and encourages other investigators to use these techniques to improve recruitment. Recruitment for all clinic sites will be discussed during all Executive Committee meetings until recruitment is closed. Monitoring of follow-up rates is handled in a similar way as recruitment.
- Responding to all inquiries from news agencies, professional groups, and other organizations about the study. The Office of the Chair responds whenever dissemination will be of greater than local scope. Clinical Center Principal Investigators may supply information only when the request is from a local organization **and** the question is factual in nature.

##### 12.3 Coordinating Center

The Coordinating Center contributes to the success of the trial in fully evaluating the effects of the treatment regimens through leadership, organization, communication, and facilitation of

the execution of the trial protocol. It is the Coordinating Center's 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 provides expertise on study design, statistical analysis, data processing and management, and coordinates the selected activities needed to carry out the study.

### **12.3.1. Location and Staff**

The CATT Coordinating Center is located in Philadelphia, Pennsylvania within the Department of Ophthalmology at the University of Pennsylvania. Statistical, epidemiologic, and data processing expertise are provided by Coordinating Center staff through the Department of Ophthalmology. Investigative and clerical personnel are employed to collect, process, and analyze the data for CATT.

A detailed description of the responsibilities and procedures related to the Coordinating Center may be found in Chapter 16. In general the activities of the Coordinating Center are to:

- Work with the other members of the study to further refine the study design;
- Provide the infrastructure necessary to support the conduct and monitoring of the study;
- Create and maintain the study database through design of data collection forms, data capture and processing, and data editing;
- Monitor all Clinical Centers for adherence to the study protocol;
- Serve as a resource to Clinical Center staff for issues concerning study protocol and procedures;
- Check on the completeness and quality of all data and to periodically distribute reports to participating clinics on delinquent forms, incomplete forms, etc.;
- Provide timely, regular reports to the Clinical Centers, Photograph Reading Center, OCT Reading Center, Executive Committee, and Data and Safety Monitoring Committee concerning study progress and performance;
- Serve as a liaison between the Drug Distribution Service and the Clinical Centers;
- Provide interim and final statistical analysis of the accumulated data;
- Design and implement a full program of quality assurance activities;
- Participate actively with the preparation of scientific reports;
- Administer Purchased Services Agreements with the Clinical Centers;
- Visit each of the Clinical Centers at regular intervals;
- Assist in training Clinic Coordinators in study procedures;
- Assist in training, certifying, and re-certifying Refractionists and Visual Acuity Examiners in the CATT protocol;

- Prepare and distribute patient recruitment and retention aids for use at the Clinical Centers;
- Prepare annual reports on the status of the study for the National Eye Institute.

In general, the Coordinating Center is responsible for coordinating and/or organizing all study activities involving the Coordinating Center, the Reading Centers, the Clinical Centers, the Executive Committee, the Clinic Monitoring Committee, and the Data and Safety Monitoring Committee. See Chapter 16 for a detailed discussion of Coordinating Center procedures and responsibilities during each phase of the CATT Study.

## **12.4 Fundus Photograph Reading Center (FPRC)**

The CATT Fundus Photograph Reading Center (FPRC) is responsible for the evaluation of retinal photographs of all patients entered into the study to determine eligibility of the patients and follow-up status of all study eyes.

### **12.4.1. Location**

The FPRC is located in Philadelphia, Pennsylvania within the Department of Ophthalmology at the University of Pennsylvania.

### **12.4.2. Functions**

Some of the specific functions of the FPRC are as follows:

- To determine on the basis of photographs whether eligibility criteria for entrance into the study have been satisfied;
- To notify the responsible clinic directly if a patient is declared ineligible on the basis of photographs;
- To evaluate retinal photographs of all study patients to determine the follow-up status of study eyes;
- To certify fundus photographers as competent in the protocol procedures;
- To assess the quality of color fundus photographs and fluorescein angiograms;
- To notify the Coordinating Center if a clinic fails to adhere to the photography protocol;
- To receive and store images of all fundus photographs and fluorescein angiograms of study patients.

See Chapter 17 for a detailed discussion of Reading Center procedures.

## **12.5 OCT Reading Center**

The CATT OCT Reading Center is responsible for the evaluation of retinal OCTs of all patients entered into the study to determine the follow-up status of all study eyes.

### **12.5.1. Location**

The CATT OCT Reading Center is located in Durham, North Carolina within the Department of Ophthalmology at Duke University.

### **12.5.2. Functions**

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

- To evaluate retinal OCTs of all study patients to determine the follow-up status of study eyes;
- To certify OCT Technicians as competent in the protocol procedures;
- To assess the quality of OCTs;
- To notify the Coordinating Center if a clinic fails to adhere to the OCT protocol;
- To notify the Coordinating Center of all disagreements between OCT graders and clinic staff about the follow-up status of an eye or the need for additional study treatment;
- To receive and store all OCTs of study patients.

See Chapter 18 for a detailed discussion of OCT Reading Center procedures.

## **12.6 Drug Distribution Center**

The Investigational Drug Service of the University of Pennsylvania serves as the Drug Distribution Center. The Drug Distribution Center provides Avastin<sup>®</sup> to the clinical centers. The Drug Distribution Center is responsible for acquiring Avastin<sup>®</sup> for repackaging in a manner that masks the treating ophthalmologist as to which drug is being administered. The Drug Distribution Center maintains records of all shipments and returns of unused drug and reports these transactions to the Coordinating Center, as needed.

## **12.7 Clinical Centers**

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

### **12.7.1. Clinical Center Staff and Resources**

Each Clinical Center is headed by a Principal Investigator who is a retina specialist and who represents the clinical center at meetings of the Investigative Group. Each Clinical Center 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 clinical center 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 examinations and tests are performed and submitted, and handling communications regarding data collection and submission with the staffs of the Coordinating Center, CRCU, FPRC and OCT Reading Center. Each center also



has at least one Refractionist and Visual Acuity Examiner who is not the Clinic Coordinator to provide for the masked evaluation of visual acuity, at least one photographer to take the required complement of CATT photographs, and at least one OCT technician to take the OCT required during study visits.

### **12.7.2. Clinical Center Functions**

The function of each of the clinical centers is to implement 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. See Chapter 14 for additional operational aspects of Clinical Center staff.

## **12.8 Executive Committee (EC)**

The Executive Committee has overall responsibility for directing the activities of the study. The Executive Committee is responsible for the major scientific leadership of the study; providing approval for all ancillary studies, abstracts, presentations, and papers; making changes in the study protocols, and advising on matters of publicity and recruitment. The committee meets twice a year - once in conjunction with the Investigative Group. Other meetings may be by teleconference or in-person.

### **12.8.1. Membership**

Members of the Executive Committee are the Study Chair (who also serves as Chair of the Executive Committee), the Study Vice-Chair, the Principal Investigators of the Coordinating Center, Fundus Photograph Reading Center and OCT Reading Center, the Director of the Fundus Photograph Reading Center, the Director of the Coordinating Center, the NEI Project Officer and five representatives of the CATT Clinical Centers (4 ophthalmologists and 1 clinic coordinator). Only clinics actively engaged in all aspects of patient recruitment, treatment, and follow-up are eligible for representation on the Executive Committee. The Study Chairman may at his discretion, and with the approval of the Operations Committee, appoint additional members to the committee, whose expertise would enhance the work of the EC. Other study personnel or individuals may be invited to attend one or more Executive Committee meetings at the discretion of the Committee or Study Chair.

### **12.8.2. 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 approve major changes in the *CATT 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 Centers;

- To approve management plans developed by the CATT Study Chair, Vice Chair, and Director of the Coordinating Center for conflict of interest when CATT Investigative Group members have a significant financial interest;
- To review appeals by investigators concerning the decisions by the CATT Study Chair, Vice Chair, and Director of the Coordinating Center concerning significant financial interests;
- 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. Any clinic that is behind schedule in meeting its recruitment goals, whose fundus and/or fluorescein photographs are consistently judged unsuitable by the Photograph Reading Center, whose OCT images are treatments are consistently judged inadequate by the OCT Reading Center, or that fails to adhere to protocol according to reports 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 13.
- To approve ancillary studies and to monitor the progress of those approved.
- To supervise the dissemination of study results;
- To appoint subcommittees as necessary.

## **12.9 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 study centers, and publicity are typically addressed by this committee. In general, changes to the protocol will not be made without convening the Executive Committee.

### **12.9.1. Membership**

The members of the Operations Committee are the Study Chairman, the Study Vice Chairman, the NEI Project Officer, the Principal Investigators of the Coordinating Center, Fundus Photograph Reading Center and OCT Reading Center, the Director of the Coordinating Center, the Director of the Fundus Photograph Reading Center and the Project Manager of the OCT Reading Center. Other people may be asked to participate on a consultative basis at the discretion of the Study Chairman. on an as needed basis. The Study Chairman will chair the Operations Committee.

### **12.9.2. Meetings**

Early in the study period, meetings of the committee will be scheduled on a weekly basis. Later, the meetings may be less frequent, but at least monthly. Most meetings will be held by teleconference. The agendas for the meetings will be provided by the Coordinating Center with input from the Chairman's Office.

## **12.10 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 Good Clinical Practices and with established standards for certification of clinic staff and timeliness of activities (Knatterud, 1998). The Committee implements the quality assurance programs described in Chapter 11.

### **12.10.1. Membership**

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

### **12.10.2. Functions**

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

- To visit each clinical center early in the enrollment phase to ensure 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 to review operations, to certify new staff, to re-certify CATT Visual Acuity Examiners and Refractionists and to review any special problems and explore ways to correct them;
- To monitor visual acuity 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 testing set-ups when changes are made in clinic facilities;
- To communicate with each Clinic Coordinator triannually to review staff changes and clinic problems;
- To schedule and organize training sessions for participating ophthalmologists, Clinic Coordinators, Refractionists, Visual Acuity Examiners, Photographers, and OCT Technicians 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 Centers 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.

- To develop and distribute individualized Clinic Report Cards highlighting the clinical center's performance in key areas.

### **12.10.3. Meetings**

The Clinic Monitoring Committee conducts committee business via email and personal communication. On a quarterly basis, the committee Telephone calls, emails, and written communications are used to transact committee business between meetings.

### **12.10.4. Protocol Monitor**

The Protocol Monitors at the Coordinating Center are responsible for reviewing adherence to the study protocol and evaluating each clinical center's effectiveness in attaining study goals. The Protocol Monitors observe clinic operations during regularly scheduled site visits, prepare written reports, and discuss observations with the Executive Committee as well as with the clinic staff. These individuals are key members of the Clinic Monitoring Committee.

## **12.11 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.

### **12.11.1. Membership**

Members include the Principal Investigators, Ophthalmologists, Clinic Coordinators, Refractionists, Visual Acuity Examiners, Fundus Photographers and OCT Technicians at the clinical centers; all members of the Executive Committee, and personnel in the Chairman's Office, Coordinating Center, Fundus Photograph Reading Center, OCT Reading Center and the representative of the NEI.

### **12.11.2. Meetings**

The Investigative Group meets once each year to review the progress of the study and to solve problems that have arisen in implementing 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 study may be invited by the Chair, but only if exceptional circumstances arise requiring their attendance for the benefit of the study. These meetings are an essential part of the quality assurance program in maintaining good communications among all study components, reinforcing difficult aspects of the protocol, and emphasizing the importance of the study.

## **12.12 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). The DSMC is advisory to the NEI. The DSMC will follow the guidelines put forth by NEI in the "National Eye Institute Guidelines for Data and Safety Monitoring of Clinical Trials" dated March 26, 2001 (NOTICE: EY-01-002).

Results of all data analyses involving comparisons of treatment groups are first presented to the Data and Safety Monitoring Committee unless this committee has given other instructions. Results are not available to the participating ophthalmologists who are treating patients until the Data and Safety Monitoring Committee decides to release the information.

#### **12.12.1. Membership**

The Data and Safety Monitoring Committee (DSMC) is appointed by NEI officials. The DSMC voting membership consists of three ophthalmologists, two biostatistician/epidemiologists, two physician specialists in cardiovascular medicine or angiogenesis and a patient advocate as voting members (total 8). The NEI representative serves as an ex officio member.

DSMC voting members may not be involved in the study, nor have a vested interest in its outcome, have ties to the study investigators (e.g., no history of extensive collaboration), nor financial ties to any commercial concerns likely to be affected by the study's outcome. If at any time a DSMC member perceives that he/she or another member of the Committee has a potential conflict of interest, he/she is obligated to bring the issue to the attention of the full DSMC for open discussion and resolution. DSMC members will complete a conflict of interest disclosure form and a statement of confidentiality before their first meeting. The Chair of the Data and Safety Monitoring Committee may appoint additional members as appropriate, who have additional expertise in patient safety, confidentiality, and medical ethics.

Executive sessions of the voting members only may be held as deemed necessary by the Chairman of the Data and Safety Monitoring Committee.

#### **12.12.2. Responsibilities**

NEI guidelines provide specific responsibilities for the DSMC. The DSMC is responsible for assuring that study patients are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards. Specifically, the DSMC will:

- Assess the performance of the trial with respect to patient recruitment, retention and follow-up, protocol adherence, and data quality and completeness, to help ensure the likelihood of successful and timely trial completion.
- Monitor interim data regarding the safety and efficacy of the study treatments, so that the trial will be concluded as soon as there is convincing evidence of the treatment effects.
- Review and consider any protocol modifications or ancillary studies proposed by the Study investigators after the main trial begins to ensure that these do not negatively impact on the main trial. Addition of an ancillary study could burden the study patients so much that they are apt to discontinue participation in the trial.

Protocol modifications will be considered in the context of their potential impact on scientific integrity and subject safety.

- Advise the NEI and the study investigators as to whether a protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.

### **12.13 Medical Safety Monitor**

The Medical Safety Monitor is responsible for ongoing monitoring of reports of SAEs submitted by the clinical centers to ensure good clinical care and to quickly identify safety concerns. A physician specialist in cardiovascular medicine will serve in this role. The Medical Safety Monitor may suggest measures to prevent the occurrence of particular adverse events, and with assistance from the Coordinating Center, will prepare regular reports concerning Serious Adverse Events. (For more information on SAE reporting, see Chapter 6). In the event of unexpected SAEs or an unduly high rate of SAEs, the Medical Safety Monitor will promptly contact the Study Chairman and the NEI representative, who will notify the DSMC Chairman. The DSMC may convene a meeting or teleconference of the Committee to consider the concerns and plan appropriate action.

**EXHIBIT 12-1**

**CATT COMMITTEE STRUCTURE**

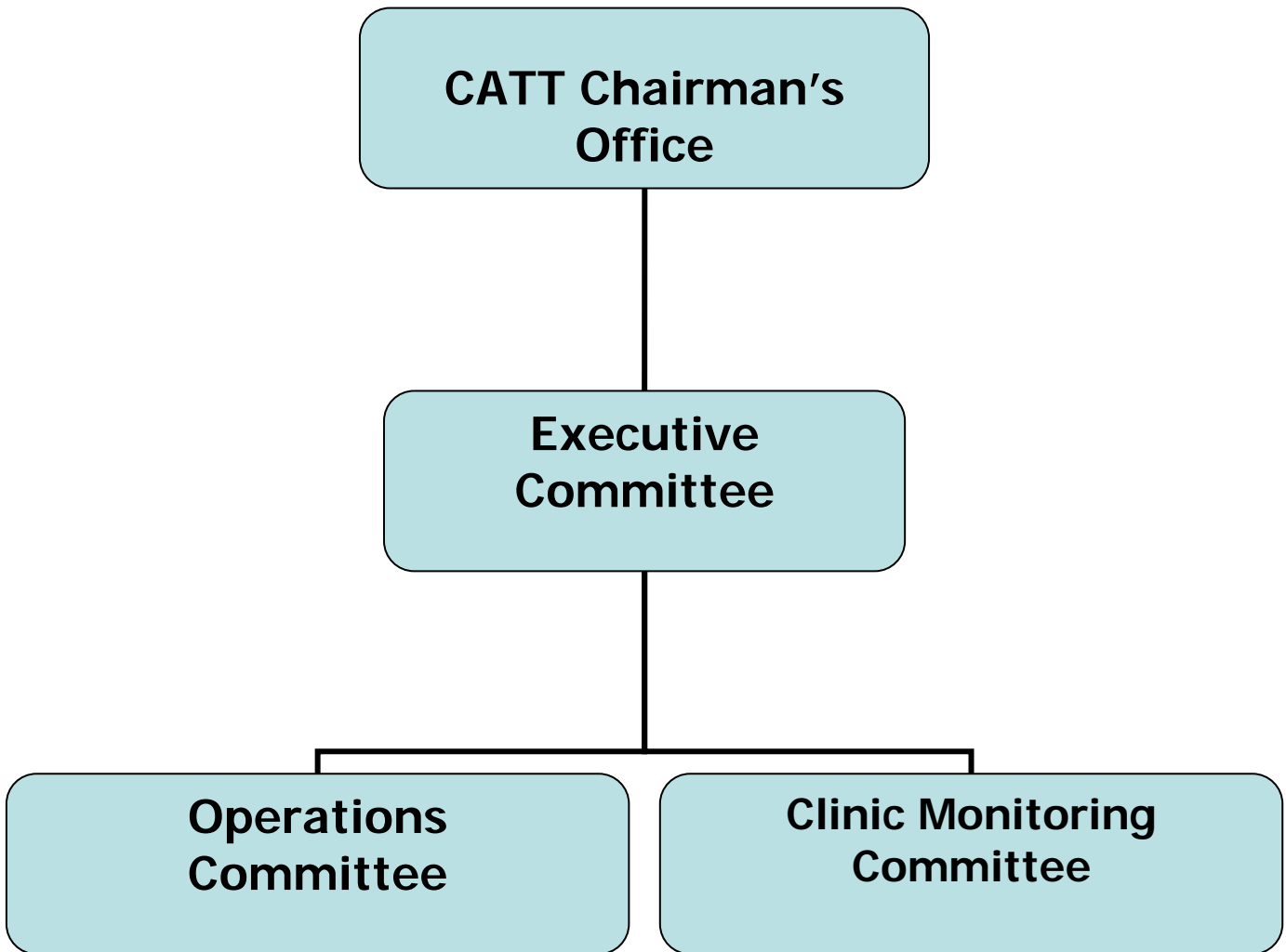
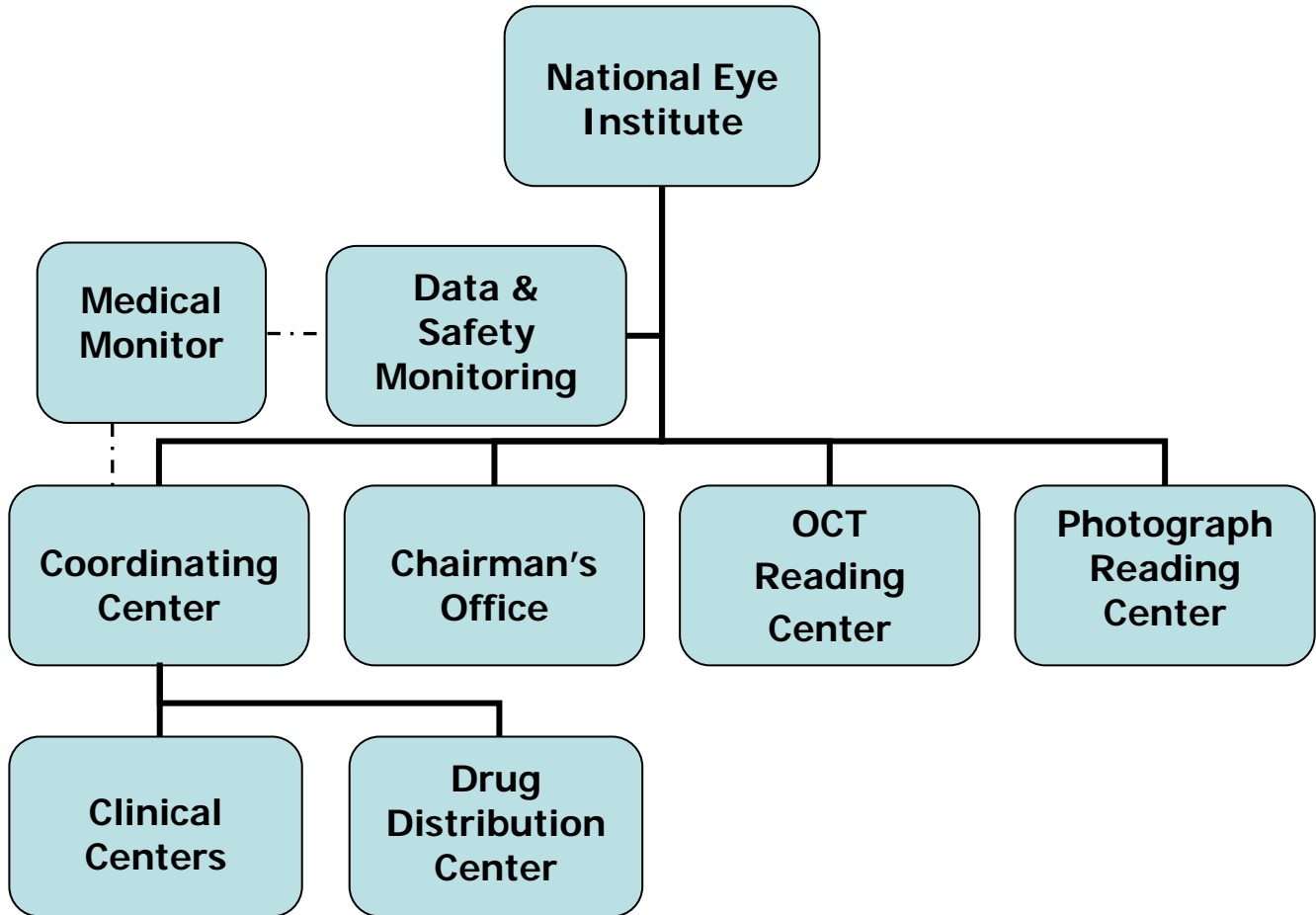


EXHIBIT 12-2

ORGANIZATIONAL STRUCTURE OF THE CATT STUDY





## CHAPTER 13

### STUDY POLICIES

#### 13. Protection of Human Subjects

The protection of patients participating in the CATT: Lucentis-Avastin Trial has been paramount in the design and implementation of the study. This includes consideration of the risks and benefits of participation, plans for the consent process, and inclusion and exclusion criteria.

##### 13.1 Institutional Review Board Review and Informed Consent

Each patient must provide written informed consent in order to participate in the Study. The consent form is prepared locally based on a prototype provided by the CATT Coordinating Center and is submitted to the local IRB for approval. (See Exhibit 13-1 for the template consent form.) All consent forms must be fully HIPAA compliant. Each participating Clinical Center must provide the Coordinating Center with a copy of the approved form before the site is certified to enroll patients into the Study.

Consent must be obtained from each patient prior to performing any study-specific procedures. Clinical Center staff may obtain verbal consent from the patient to perform study-specific procedures, such as a protocol refraction and visual acuity test. The fact that verbal consent is obtained should be noted in the patient's chart. A script for obtaining verbal consent is provided to the Clinical Centers by the CATT Coordinating Center (see Exhibit 13-2). Clinical Centers must obtain approval for the verbal consent process and the script from their local IRB. If the patient is determined to be eligible after all screening tests have been performed, WRITTEN informed consent must be obtained from the patient before enrollment into CATT.

Informed consent must be documented through the signature of the participating patient on the locally approved consent form. A copy of the signed/dated consent must be provided to the patient and the original will be maintained at each Clinical Center. The signed consent form must be available for inspection during site visits.

Investigators at each center are responsible for conducting the consent process, describing study procedures, discussing the risks and benefits and alternatives to participation, and discussing the voluntary nature of participation with the potential subject. The patient should be asked to sign the consent form only after the patient has been introduced to the study and had all questions answered to his or her satisfaction.

All investigators and clinic staff must complete training programs in ethics and maintaining the safety of human subjects in clinical research and in complying with HIPAA regulations prior to becoming eligible for CATT certification. Training may be provided by the individual institutions' approved training program or by the NIH website. If the local institution requires additional training for those engaged in human research at their institution, this too must be completed before commencing with any CATT procedures. Certificates documenting the successful completion of ethics and patient safety programs must be submitted to the Coordinating Center by all members of the investigative group prior to CATT certification.

### **13.1.1 Patient Confidentiality**

Participating Clinical Centers must take all appropriate measures to protect the confidentiality of CATT patients. All scans, photographic materials and study forms that leave the Clinical Center do not identify the patient by name. Patients are assigned a unique numeric and letter code that is not related to their birth date, social security number or name. All study materials are kept in locked file cabinets at the Coordinating Center, OCT Reading Center and Fundus Photograph Reading Center. Patient identities are not to be revealed in any publication that may result from this Study. The participating Clinical Centers maintain a log of patients' names, social security numbers, and assigned patient ID numbers, which are kept in a locked cabinet. Clinical information is not to be released without written permission of the patient, except as necessary for monitoring by the IRB, FDA, the NEI, the OHRP, and Protocol Monitors.

### **13.2 Patient Costs**

Patients do not pay any charges for study drugs. Lucentis® is supplied to Study patients by the clinical center using the same supply system as used outside of the Study. Claims for Lucentis® are to be submitted to Medicare, or the patient's primary insurance if different from Medicare. Claims are also submitted to the patient's supplemental insurance for the co-pay not covered by Medicare or other primary insurance. Any residual payment due for Lucentis® after all secondary and supplemental insurance payments have been made is covered by Study funds. Avastin® is supplied by the Study at no cost to the clinical center or patient.

Charges for Study office visits, imaging, and injection fees are the responsibility of the patient, Medicare, or the patient's other insurance. The frequency of visits and procedures within the CATT: Lucentis-Avastin Trial are within the norms of standard care for patients with neovascular age-related macular degeneration. In addition, insurance companies will be charged for any treatment for side effects that may occur as a result of participation in the study.

### **13.3 Publicity**

All publicity and press releases on behalf of the CATT: Lucentis-Avastin Trial are to have prior approval of the Executive Committee. CATT investigators who are approached by the press for information concerning the study should refer these inquiries to the Study Chairman. 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 the CATT: Lucentis-Avastin Trial. 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.

During the recruitment phase of the study, announcements (pre-approved by the CATT Executive Committee) may be placed in local media (newspaper, radio, television). The Coordinating Center also prepared for each clinical center a set of slides to present at local professional society meetings to aid in recruitment and study visibility. On a national level, study publicity will be increased by postings on the NEI and ClinicalTrials.gov web sites, and by mailings to AMD patient organizations.

## **13.4 Publication Plan**

CATT: Lucentis-Avastin Trial papers are defined as those that use data, documents, or other information collected during the course of the Study. Publication of the results of CATT trials will be governed by the policies and procedures developed by the Executive Committee. The Executive Committee reviews all written reports prepared for publication.

A subcommittee of the Executive Committee ensures that the preparation of the results for abstract presentation or publication complies with NIH policies and guidelines, and appropriate analysis and conclusions are reached.

### **13.4.1 Authorship**

All reports from the Comparisons of Age-related Macular Degeneration Treatments Trials Group that involve comparison of treatment groups and/or the major outcome measures of CATT studies will list the “Comparisons of Age-related Macular Degeneration Treatments Trials Group (CATT)” as author. All professional participants of the Group are listed at the end of each paper and are considered as contributors. In addition, all CATT 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

### **13.4.2 Manuscript Writing Teams**

The CATT Operations Committee will determine potential manuscript topics based on interim analyses and hypotheses. Investigative Group members are invited to volunteer for writing assignments and to suggest additional topics where appropriate. The Coordinating Center solicits members for the writing committees for CATT papers from among the CATT Investigative Group. Final designation of the writing committee will be made by the chair of the writing committee. The Executive Committee may recommend particular members of the Investigative Group for inclusion in the writing committee of specific papers. Along with the Operations Committee, each writing team will select the journal to receive the submission.

### **13.4.3 Manuscript Pre-Submission Review**

Papers prepared for publication must be sent to the CATT Chairman or to the Coordinating Center Director for review and advance approval by the Executive Committee. If approved by the Executive Committee, the manuscript is then sent to the Data and Safety Monitoring Committee (DSMC) for review and approval.

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. The DSMC, at their initial meeting, may also decide to mandate their review of oral presentations and abstracts in advance. 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 CATT: Lucentis-Avastin Trial, provided these presentations contain no unpublished Study results. Such presentations are encouraged to stimulate recruitment.

Copies of Study 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 members of the DSMC and to each center for distribution among the staff.

Manuscripts emanating from ancillary studies must be sent to the Executive Committee for review before submission for publication. See also Section 13.6.

#### **13.4.4 Acknowledgements**

Each publication must acknowledge support from the National Eye Institute (NEI).

#### **13.5 Data Sharing**

NIH released “Final NIH Statement on Sharing Research Data” (NOT-OD-03-032) on February 26, 2003 which modified “NIH Announces Draft Statement on Sharing Research Data” (NOT-OD-02-035). In accord with NIH guidelines, a summary, de-identified data set will be made available through the CATT website at the time of publication and through direct inquiries to the Study Chair or Coordinating Center. The CATT data sets will be largely self-documenting in that an item identifier is embedded within the label for each variable. In addition, key derived variables will also be contained in the data sets.

The rights and privacy of people who participated in the Study will be protected at all times by stripping the data from all identifiers that could lead to disclosing the identity of individual research participants. This commitment to privacy-protected data sharing will be incorporated in all levels of database design.

By the end of the funding period, de-identified SAS data sets and form images corresponding to all data collection forms used, as well as key derived variables, will be put on file with a data repository such as the National Technical Information Service (NTIS).

The full SAS databases (not de-identified) associated with CATT will be kept on secured computer systems maintained by the Study Chair and by the Director of the Coordinating Center. Researchers may request limited access data sets and will need to enter into a data sharing agreement. Guidelines for the process of requesting such data sets and their content have been put forth recently by NHLBI (Geller, 2004). Access to the CATT database will be similar to these guidelines. Researchers requesting limited access data sets will bear the cost of their preparation.

#### **13.6 Ancillary Studies**

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 the CATT and ensure the continued interest of many capable investigators. However, to protect the integrity of the CATT, such ancillary studies must be reviewed and approved by the Executive Committee and Data and Safety Monitoring Committee before their execution, whether or not they involve the need for supplementary funds.

### **13.6.1 Definition of a CATT Ancillary Study**

An ancillary study is a research study that requires either

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

### **13.6.2 Reasons for Requirement of Approval**

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

- Complicate the interpretation of the CATT results;
- Adversely affect patient cooperation;
- Jeopardize the public image of CATT;
- Create a serious diversion of CATT resources locally or at the Resource Centers.

### **13.6.3 Preparation of Request for Approval of a CATT Ancillary Study**

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 CATT 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 Clinical Center 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.

### **13.6.4 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.

### **13.6.5 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 activate the ancillary study until approval has been received from the CATT Executive Committee and DSMC.

### **13.6.6 Publication of Ancillary CATT Results**

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

### **13.6.7 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.

### **13.7 Related Studies**

Individual CATT investigators who carry out studies related to ongoing, completed, or proposed CATT studies should be aware that their conclusions and interpretations might be viewed by non-CATT investigators as reflecting the position of the CATT Group. The study may be related because of types of patients included, types of treatment evaluated, or similarity of methods to those used in the CATT Study. 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 CATT Study are not jeopardized.

### **13.8 APPROVAL OF CHANGES IN PROTOCOL**

All significant changes to the CATT protocol must be approved by the CATT Operations Committee, Executive Committee and the DSMC. In some circumstances, approval from NEI may also be required. When a change in protocol is implemented, a protocol memorandum will be issued to clinical center staff. All CATT clinical center staff will be required to acknowledge receipt of the protocol memorandum and that they understand its contents by signing and dating a form that is sent to the Coordinating Center. During site visits, the Protocol Monitor reviews whether all CATT protocols, forms and other documents are up to date.

#### **13.8.1 Changes to the Manual of Procedures**

The CATT Manual of Procedures will be revised to reflect changes to the protocol. All revised manual chapters are distributed by the Coordinating Center. Any revisions to chapters that originate in other CATT resource centers (i.e., the OCT Reading Center or Fundus Photograph Reading Center) must be sent to the Coordinating Center for distribution to the clinical centers.

**EXHIBIT 13-1**

**University of Pennsylvania**

**Research Subject  
Informed Consent Form**

**Protocol Title:** CATT: Lucentis-Avastin Trial

**Principal Investigator:** **Insert Name of the Principal Investigator**  
**Address**  
**Insert Phone Numbers**

**Sponsors:** **National Eye Institute (NEI)**

**Emergency Contact:** **Insert Emergency Contact**  
**Insert Phone Number/Pager, etc.**

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**Why am I being asked to volunteer?**

You are being asked to participate in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT): Lucentis-Avastin Trial, a randomized clinical treatment trial, because you have previously untreated, active, subfoveal choroidal neovascularization (CNV) secondary to Age-related Macular Degeneration (AMD) (also known as neovascular or “wet” AMD), you are at least 50 years of age and you meet other requirements for enrollment into this study. Your participation in this study is voluntary, which means that you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do to participate. The ophthalmologist (eye doctor) who is working on this study and his/her study assistant (the study coordinator) will explain the study to you, and have given you this consent form to read. You may also decide to discuss it with your family, friends or your personal doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the study coordinator to explain any words or sections of this form you do not understand. If you decide to participate, you will be asked to sign this form and will be provided a copy for your records.

**What is the purpose of this research study?**

Neovascular (wet) AMD is one of the leading causes of vision loss in people aged 60 and older. The purpose of the Lucentis-Avastin Trial study is to compare two drug treatments for neovascular “wet” AMD for their effects on vision and for safety. The two drugs being compared are Lucentis® (ranibizumab) and Avastin® (bevacizumab). The study is sponsored by the National Eye Institute (NEI), a branch of the National Institutes of Health, an agency within the U.S. Government.

### **What is Lucentis®?**

Lucentis® is a drug that was approved by the U.S. Food and Drug Administration (FDA) in 2006 to treat “wet” AMD. Lucentis® interferes with the growth of new vessels and prevents leakage of fluid from new blood vessels. The clinical trials that showed the best results for Lucentis® called for an injection of a small amount (0.5 mg) of Lucentis® into the eye every four weeks. Lucentis® costs approximately \$2100 per injection.

### **What is Avastin®?**

Avastin® is a drug that has been approved by the FDA for the treatment of cancer. Patients with cancer have Avastin administered to them through a vein in their arm. Avastin® interferes with the growth of new vessels and prevents leakage of fluid from new blood vessels. It has NOT been approved to treat AMD; however, many doctors have been injecting it into the eye to treat AMD. Avastin® costs approximately \$50 per injection.

### **What exactly will the study compare?**

Avastin® and Lucentis® have similar actions, but it is not known whether Avastin® is more effective, less effective or the same as Lucentis® for treating AMD. Also, doctors want to know whether treating less frequently than every four weeks can provide the same benefits as treating every 28 days. This study will compare four (4) treatment plans for AMD:

- 1) An injection into the eye of 0.5 mg.(0.05ml) of Lucentis® given every four weeks
- 2) An injection into the eye of 1.25 mg (0.05ml) of Avastin® given every four weeks
- 3) An injection into the eye of 0.5 mg. of Lucentis® given on the advice of your study doctor. The study doctor’s decision is based on an examination of your eye and on other clinical test results that can indicate CNV is active.
- 4) An injection into the eye of 1.25 mg of Avastin® given on the advice of your study doctor. The study doctor’s decision is based on an examination of your eye and on other clinical test results that can indicate CNV is active.

Both Lucentis® and Avastin® are given by injection into the vitreous of the eye through the sclera. (The sclera is the “white of the eye” and the vitreous is the clear, jelly-like substance in the middle of the eye.) The procedure is called an “intravitreal injection”.

### **How long will I be in the study? How many other people will be in the study?**

You will be in the study for two years of treatment. The study will include the initial visit and follow up office visits that are scheduled every four weeks for two years. There will be 1200 patients participating in this study in approximately 45 clinical centers (doctor’s offices) throughout the United States. Each of the four treatment groups will have a total of 300 participants.

### **What am I being asked to do?**

Your consent to participate in this study means that you agree to be treated according to one



of the four study treatment plans. Your treatment plan will be selected randomly, like the flip of a coin, from among the four treatment plans rather than having your treatment selected by your study doctor and you. Everyone in the study will receive some kind of treatment. We do not know which treatment is best.

If you are randomized into one of the groups that receives injections every four weeks, you will continue this treatment schedule for one (1) year. At the end of one year you will again be randomly assigned to either treatment every 4 weeks for the next year or treatment only when your study doctor decides that the CNV is active. The same drug that you were originally assigned to, either Lucentis<sup>®</sup> or Avastin<sup>®</sup> will be used during the second year.

If you are assigned initially to treatment only when your study doctor decides that the CNV is active, your treatment will continue this way for two years.

Your study doctor and the person who will test your vision will not know which study drug (Lucentis<sup>®</sup> or Avastin<sup>®</sup>) you are being given. This is done so that that this knowledge cannot influence the results of vision testing and treatment decisions. However, for safety reasons, information on which drug you are receiving will be available to your doctor if medically necessary. You will not be told by the study team about which study drug you have been assigned. You may learn which drug you are receiving from billing and insurance statements. If this happens and you have questions about your billing, we ask that you speak only to the study coordinator about your statements and study drug.

Whether or not you choose to participate in this study, there is an approximate 10% chance per year that your other eye will develop CNV if it has not already done so. In that case, we would encourage you to speak with your study doctor and with your personal doctor about the choices for treatment of your other eye.

### **What happens during study visits?**

You will have an eye doctor's visit every four weeks for two years. At **all** study visits, you will be examined by an ophthalmologist (an eye doctor) who will check how your eye is doing and you will have your vision tested. At each clinic visit you will also be questioned about your health and the medications you are taking. If you have been hospitalized, we will ask for your hospital records. Other tests will be done at all or some of the study visits. Patients assigned to receive treatment only when the study doctor decides that CNV is active will undergo a procedure called "Optical Coherence Tomography" or OCT at every visit. An OCT is a quick, painless, non-invasive procedure that scans the inside of your eye. Patients assigned to treatment every 4 weeks will have an OCT for their first 4 study visits and then at 6, 12, 18, and 24 months.

At the first study visit and at 3, 6, 12, 18, and 24 months, you may have eye photographs taken and a fluorescein angiogram. A fluorescein angiogram is a procedure in which fluorescein dye is injected into a vein in your arm and special pictures that show blood vessels are taken of your eye.

If you have been assigned to the treatment groups that receive treatment every four weeks, you will receive treatment at all study visits. If you have been assigned to the treatment groups that receive treatment only when your study doctor decides that the CNV is active, you will be treated only if the CNV appears active. After the first time you are treated, you will receive a telephone call from the Clinic Coordinator within 3-5 days, to see if you are experiencing any problems from the treatment.

### **What are the possible risks or discomforts?**

During your participation in this study, you are at risk for the side effects described below. You should discuss these with the study doctor. There may also be other side effects that we cannot predict. Other medicines may be given to lessen the side effects and discomfort. Many side effects go away shortly after you stop treatment, but in some cases, side effects can be serious, long lasting, or permanent.

### **Possible Risks Associated with Lucentis® and Avastin®**

Both Lucentis® and Avastin® have been studied in humans in **previously** completed clinical trials and research studies. The following side effects have been observed in treatment with each drug: temporary redness of the injected eye, minor bleeding at the injection site that resolves on its own (doesn't require treatment), dull pain in the injected eye, sensitivity to light, mild and temporary burning and stinging, vision disturbances, including decrease in vision, bleeding inside the injected eye that resolves on its own, infection outside the treated eye, and mild and self-resolving inflammation on the inside of the eye. Injection of the numbing medication may lead to minor bleeding under the surface of your eyeball; the bleeding will usually stop on its own, and the surface of your eye should return to its usual appearance. Antiseptic cleaning of the eye is done before each injection to minimize the risk of infection.

Less frequent side effects include infection inside the eye (endophthalmitis) severe inflammation in the inside of the eye (uveitis), blockage of the blood flow in the main vein inside the eye (central retinal vein occlusion), temporary increase in the pressure inside the eye (intraocular pressure), damage to the lens inside the eye (cataract formation), a tear through the retinal tissue in the eye (retinal tear/detachment), a rip in the pigment cell layer that lies beneath and nourishes the retina (retinal pigment epithelial [RPE] tear) and inadequate response of the pupil to light entering the eye. Some of the complications listed above may result in permanent loss of vision or loss of the eye.

If you have a history of glaucoma, you may be at more risk for experiencing increased pressure within your eye after an injection of any substance, including Lucentis® and Avastin®. To participate in this study, it must be shown that your glaucoma is well controlled with medication and that you take your medication as it has been prescribed by your doctor.

There is a chance that your vision may worsen. Worsened vision could be due to progression of your AMD, to a side effect of Lucentis® and Avastin® injection, or for other reasons. There is a chance that you will experience an allergic reaction to Lucentis® and Avastin®. Allergic reactions may be mild, such as skin rash or hives, or severe, such as breathing difficulties or shock. A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death. An allergic reaction can also cause a red, dry or itchy eye. It

is not possible to predict in advance if any of these problems will develop, but if they do, you will be promptly treated.

Tests have shown that low levels of Lucentis<sup>®</sup> and Avastin<sup>®</sup> can reach your blood stream after injection into the eye. The significance of this is not well understood. However, in one recent study, 1.2% of the people who took 0.5 mg of Lucentis<sup>®</sup> injected into the eye every 4 weeks developed stroke while only 0.3% of those who had an injection of a lower dose (0.3 mg) had a stroke. Among those people who had a history of prior stroke, the risk for another stroke was higher than among those with no prior stroke. The risk of having another side effect involving a body system other than the eye is unknown but is believed to be very small. Additional serous side effects have been associated with Avastin when it is given at high levels (more than 300 times the amount injected into the eye) directly into the blood stream for cancer patients. Strokes, transient ischemic attacks (TIAs), heart attacks, and angina (heart-related chest pain) were 2 to 3 times more common in cancer patients receiving Avastin<sup>®</sup> than in cancer patients not receiving Avastin<sup>®</sup>. In addition, intestinal perforations, wound healing complications, bleeding, high blood pressure, protein in the urine, infections, and congestive heart failure have been more common in cancer patients receiving Avastin<sup>®</sup>.

As is true for any drug, unknown and potentially serious or life-threatening side effects could occur with Lucentis<sup>®</sup> and Avastin<sup>®</sup>.

### **Risks on fetuses**

The effects of Lucentis<sup>®</sup> and Avastin<sup>®</sup> on a fetus (unborn child) are unknown and may be harmful; therefore, females should not become pregnant while in this study. To participate in this study, females who are capable of bearing children must agree to use an effective, medically accepted method of birth control to prevent pregnancy and will be required to take a pregnancy test before entry into this study. If you are pregnant, you cannot be in this study because of possible harm to the fetus. If at any time during the study you suspect that you have become pregnant, you must notify the study doctor immediately. If after your participation in the study is over, you suspect that you have become pregnant within 90 days of the last administration of study drug, you must notify your study doctor immediately. Further, you understand that if you do become pregnant, you must stop study treatment. You must not breast feed a baby while in this study because Lucentis<sup>®</sup> and Avastin<sup>®</sup> may enter breast milk and possibly harm your child.

### **Risks and discomfort associated with Optical Coherence Tomography (OCT)**

OCT takes approximately 10 minutes to perform. It is non-invasive and is not painful. No radiation is used. You will sit at a machine and look straight ahead as the machine takes pictures of the back of your eyes. No side effects from this test have been reported.

### **Risks and discomfort associated with fluorescein angiography**

Patients having a fluorescein angiogram sometimes have side effects from the injection of the dye into the vein in their arm. Side effects include nausea and/or vomiting (5% risk), hives and itching (0.5% risk), and rarely a life-threatening allergic reaction (<0.01% risk).

## **POTENTIAL BENEFITS**

Previous studies have shown that an intravitreal injection of Lucentis<sup>®</sup> every 4 weeks leads to much less loss of vision when compared to people not treated with Lucentis<sup>®</sup>. Intravitreal injections of Avastin<sup>®</sup> may provide similar beneficial effects. In addition, your participation in this study means that you will have the benefit of receiving treatment for AMD without any out-of-pocket expense to you for the drug, although Medicare and/or your insurance will be billed. Your participation in this study may lead to new treatment standards for people who have “wet” AMD.

### **What if new information becomes available about the study?**

An independent committee of physicians, statisticians and patient advocates (known as a Data and Safety Monitoring Committee) will review the study findings while the study is ongoing. The committee will keep the results confidential unless there is new important information on the study drugs. The committee will disclose findings to the study doctors when there is new information on the safety of the study drugs or when there is proof beyond a reasonable doubt that one treatment is better than the other. We will notify you as soon as possible if such information becomes available. In addition, if information from other studies becomes available during your participation in this study, we will notify you as soon as possible.

### **What other choices do I have if I do not participate?**

Your participation in this research study is voluntary. Instead of participating in this study, you may choose a specific treatment plan after discussion with your doctor. Both Lucentis<sup>®</sup> and Avastin<sup>®</sup> are routinely available to your eye doctor outside of this study. Your doctor will discuss your options with you. You may want to discuss your choice with your family, friends and/or your personal physician. Your choice not to participate in this study or will not affect your medical care in any way.

### **Will I be paid for being in this study?**

There will be no payment or compensation for your participation.

### **Will I have to pay for anything?**

You and/or your health insurance will be billed for clinic visits, the study doctor's fee for injections, tests and other procedures outlined in this consent form as well as for the costs of medical care during this study if these expenses would have been charged even if you were not in the study. Your health insurance may be charged for the study drug. You must either be enrolled in Medicare, or have private insurance that will cover at least 80% of the charge for the study drugs, or commit to pay personally for the study drug (self-insured). If any drug charges remain after your insurance plans have paid the bill for the drug, the study will pay them. The charge for study drug may appear on your billing account while the insurance payments are being processed. However, you will not have to pay for charges for the study drug.

### **What happens if I am injured or hurt during the study?**

If you have a medical emergency during the study you may contact Dr. \_\_\_\_\_ or the emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise available from the University of Pennsylvania. If you have an illness or injury during this research trial that is not directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

### **When is the study over? Can I leave before it ends?**

This study is expected to end after all participants have completed all visits, and all information has been collected. Your participation in the study will end in 2 years, after you have completed all your study visits. You may decide to leave the study at any time before the end, and your withdrawal from the study will not interfere with your future care. Should your physician find it necessary, and/or in your best interest, he/she may withdraw you from the study treatment but will ask for you to continue to be followed as part of the study. This study may also be stopped at any time by your physician, the National Eye Institute, or the Food and Drug Administration (FDA) without your consent, but you will be informed if such a decision is made and the reason for this decision.

### **Who can see or use my information? How will my personal information be protected?**

The investigator and staff involved with the study will keep your personal health information collected for the study strictly confidential. Please refer to the separate "Confidentiality & Privacy Rights" document that explains more specifically how your personal information will be protected. Information about your AMD, vision and photographs will be submitted to researchers at the University of Pennsylvania. Your OCT scans will be sent to a Reading Center at Duke University. All your information will be labeled with only number and letter codes. When the results of the study are reported in publications, your information will be reported as part of a group. You will not be identified in any way.

Your information may be reviewed by designated representatives of the CLINICAL INSTITUTIONS, the University of Pennsylvania, the National Eye Institute, and the U.S. Food and Drug Agency (FDA) who may need to review study records to ensure the quality and integrity of data collected in this study.

### **Who can I call about my rights as a research participant?**

If you have questions regarding your participation in this research study or if you have any questions about your rights as a research participant don't hesitate to speak with Dr. \_\_\_\_\_, whose phone number is listed on page one of this form. Concerning your

rights as a research participant, you may also contact the Office of Regulatory Affairs at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in the Comparisons of Age-related Macular degeneration Treatments Trial. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your health information.

\_\_\_\_\_  
Name of Subject (Please Print)      Signature of Subject      Date

\_\_\_\_\_  
Name of Person Obtaining      Signature      Date  
Consent (Please Print)

*For Use With Authorized Representative Signature*

For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

\_\_\_\_\_  
Authorized subject      Authorized subject      Date  
representative **[print]**      representative Signature

Provide a brief description of above person authority to serve as the subject's authorized representative.

## EXHIBIT 13-2

### Script Approved by University of Pennsylvania's IRB for Obtaining Verbal Consent for Eligibility Screening

Good morning {Patient Name},

I'm {Clinic Staff Member Name}. As you know, you are going to be evaluated today to determine if you are a candidate for treatment for macular degeneration. We will perform some tests including measuring your vision, taking photographs, and obtaining an image of your macula to document the extent of fluid leakage in the macula that may be affecting your vision.

In all likelihood, you will be a candidate for treatment. There actually are two effective treatments. We are involved in a research study supported by the National Institutes of Health to compare which of these treatments might be better at preserving vision.

This study will enroll 1,200 patients at more than 45 centers across the entire U.S. If you are eligible for the study, I will describe the study in more detail and ask if you want to participate.

The first thing, however, is to measure your vision. Because we want the vision measured in patients all over the country to be standardized, I need your verbal consent to measure your vision in a standardized way. If you give me your verbal consent, there is no need to sign anything now.

#### **NOTES:**

This script is a sample. The script can be modified at your center to include other study-specific screening procedures.

The verbal consent process is optional; however, if it is not used, written informed consent for the entire study must be obtained prior to performing any study-specific procedures.

## CHAPTER 14

### CLINICAL CENTER STAFF RESPONSIBILITIES AND CERTIFICATION REQUIREMENTS

#### 14.1. OVERVIEW OF CERTIFICATION PROCEDURES

It is important that all procedures in CATT be standardized and that all individuals who are part of the CATT 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 CATT 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, Refractionist, Visual Acuity Examiner, OCT Technician and Fundus Photographer. Also, all personnel in the Coordinating Center, Reading Centers, and Chairman's Office must fulfill certain criteria. Most aspects of the certification process will be accomplished on-line via the CATT web site.

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

Everyone engaged in CATT must have core knowledge about CATT so that questions from patients and others may be answered accurately. All members of the Investigative Group must complete a General Knowledge Assessment about CATT that requires knowledge of such basic facts as the name of the study, the definition of and implications on vision of choroidal neovascularization, and the primary outcome measure. In addition, individuals are required to complete role-specific assessments, as described below.

Knowledge assessments must be completed by the original CATT group and by all new personnel at the time of hiring. The Coordinating Center Director and Protocol Monitor are responsible for reviewing the certification materials completed by Clinic Coordinators and Visual Acuity Examiners, respectively, and contacting the respondents if there are areas of misunderstanding. The Senior Technical Analyst at the OCT Reading Center is responsible for reviewing certification materials submitted by OCT Technicians, and the Director of the CATT Fundus Photograph Reading Center (FPRC) is responsible for reviewing the forms and photographic materials submitted by fundus photographers. The study Chairman or his designees at the Coordinating Center or Reading Centers is responsible for reviewing materials submitted by ophthalmologists for CATT certification. The Coordinating Center Director and Protocol Monitor maintain a log of all people who have successfully completed certification requirements.

Prior to becoming eligible for CATT certification, all investigators and clinic staff must have training in protecting the rights and welfare of human subjects involved clinical research, and in complying with HIPAA regulations. Current certificates documenting the successful completion of a Human Subjects Training program must be submitted to the Coordinating Center by all members of the investigative group prior to CATT certification.



### **14.3. RESPONSIBILITIES OF CATT OPHTHALMOLOGISTS**

The CATT Ophthalmologist is the treating physician who is responsible for the overall conduct of the CATT at her/his study site. The ophthalmologist is responsible for enrolling, treating and following CATT patients. In doing so, the Ophthalmologist determines that the patient has subfoveal CNV according to the Study criteria, performs the CATT ophthalmological evaluations at all visits, determines the need for additional study treatment in accordance with the Study guidelines, administers CATT treatment, monitors adverse effects of treatment and prescribes remedies for these problems.

### **14.4. CERTIFICATION REQUIREMENTS FOR CATT OPHTHALMOLOGISTS**

All CATT Ophthalmologists are required to have completed a retina fellowship. Ophthalmologists must have specific knowledge of the major eligibility criteria, treatment protocols, 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 and/or the study Chair do not improve performance, certification for the ophthalmologist will be revoked.

#### **14.4.1. Specific Requirements for Ophthalmologist Certification for the CATT Study**

The certification process entails fulfillment of several criteria to demonstrate knowledge and proficiency in Study procedures. To be certified, the CATT ophthalmologist must:

- Submit documentation of completed fellowship in Retina (NIH Biosketch, CV page, letter from fellowship program)
- Read specific sections of the CATT Manual of Procedures
- Attend a CATT Training meeting; or review the relevant slide presentations from the training meeting and have a brief conversation with the Study Chair
- Complete the online CATT Study General Knowledge Assessment
- Complete the online CATT Ophthalmologist's Eligibility and Retreatment-Exercise to test knowledge of eligibility criteria, treatment protocol, re-treatment guidelines and managing patients during follow-up.
- Complete the online Ophthalmologist's Knowledge Assessment
- Understand the treatment protocol and guidelines for the consideration of re-treatment

Upon successful completion of all certification requirements, a valid certification number for each ophthalmologist will be issued by the Coordinating Center.

## **14.5. RESPONSIBILITIES OF THE CATT CLINIC COORDINATOR**

Clinic Coordinators are responsible for supervising activities related to the CATT Study and integrating these with clinic operations. Coordinators are responsible for managing patient visits, paperwork and data associated with the visits, maintaining patient follow-up, and ensuring that information and materials on the CATT Study are distributed to the appropriate Study team members in the Clinical Center. Clinic Coordinators must be knowledgeable about appropriate procedures for data correction, appropriate people to call within the Coordinating and Reading Centers to answer questions, procedures for patient enrollment and treatment allocation, ensuring that the ophthalmologists have access to needed CATT Study documentation, and many other procedural requirements. At the beginning of the Study, Clinic Coordinators were required to attend a training meeting during which they received thorough instruction on their responsibilities and specific training in the administration of the standardized questionnaires they will be required to submit during the Study. Individuals who later wish to become Clinic Coordinators will need to be trained by either the previous Clinic Coordinator or through conversations with the Coordinating Center Director and Protocol Monitor.

### **14.5.1. Qualifications**

Because the Clinic Coordinator plays a pivotal role in coordinating the responsibilities of the Clinical Center, it is important that this individual be selected carefully, thoroughly trained in the CATT protocol, and recognized as the local CATT Study "expert" in the clinical center. It is essential that the Principal Investigator allocates sufficient time to the Coordinator to allow for the myriad of activities required.

The Clinic Coordinator has extensive contact with CATT Study patients; therefore this individual must have excellent "people skills". The rapport that frequently develops between a patient and the Clinic Coordinator is extremely important to assure the continued cooperation of a patient throughout the course of a Study. Thus it is mandatory that the Clinic Coordinator be a mature, responsible person with a thorough understanding of the CATT Study protocol, design, and rationale. In addition, the Clinic Coordinator must have excellent organizational skills and attention to detail.

### **14.5.2. Specific Responsibilities**

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

- To coordinate clinical site activities related to the CATT Study.
- To have a thorough understanding of the CATT Study design and methods.
- To ensure timely submissions of materials to the clinical center's IRB for approval and to ensure that approvals do not lapse during the course of the study.
- To report all serious adverse events to the appropriate entities (see chapter 6) in a timely manner.
- To schedule and coordinate patient examinations
- To maintain a supply of study drug and to reorder supplies as necessary.

- To destroy or return all expired unused study medication.
- To provide the primary interface between the clinical center, Coordinating Center and the two 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 maintain complete and current residency and employment information on each patient enrolled for the duration of the CATT Study.
- 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 distribute materials and information to the appropriate CATT Study team members.
- To coordinate use of CATT Study patient education and recruitment materials, including slides, brochures, and exhibits provided by the Coordinating Center.
- To maintain required Study documentation, including:
  - ▶ Up-to-date *CATT Study Manual of Procedures*, as provided by the Coordinating Center, with addenda in the form of protocol memoranda.
  - ▶ Scheduling notebook with a copy of the CATT Study follow-up schedule for each patient.
  - ▶ Patient Log Book, containing CATT Study identifiers (CATT number and alphabetic code), patient name, enrollment date and treatment assignment as well as the signed consent form and the patient information sheet of each patient in CATT identification number order.
  - ▶ Log of all materials sent to the Coordinating Center, Reading Centers, and Investigational Drug Service.
- To review all forms and materials for completeness and accuracy before they are submitted.
- To retain copies of all study forms 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 CATT Study case report forms maintained by the Clinic Coordinator and the other in the usual way for the Clinical Site.
- To ensure accurate and timely data entry of CATT case report forms into the Remote Data Capture system.
- To promptly respond to data system edit queries and notices from the Coordinating Center regarding information or documents provided for CATT Study patients.
- To coordinate local arrangements for clinic monitoring visits so that all CATT Study-certified personnel are available.
- To maintain a Forms Notebook containing current versions of all CATT Study case report forms.

- To notify the Coordinating Center concerning personnel changes that affect local CATT Study 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 CATT Study patients.
- To organize regular clinic staff meetings of all CATT Study personnel.
- To inform the clinic Principal Investigator of any problems with clinic management and to suggest ways to resolve them.
- To attend scheduled meetings of the CATT Study Research Group.
- To assist clinic personnel with CATT certification.
- To confirm that certification requirements for the digital imaging system have been completed.
- To explore benefit programs for patients within the local institution and learn how to facilitate patient participation in these programs, as required. These may include reduced parking charges, low cost meals, reduced room rates at local hotels, special arrangements for local transportation, etc.
- To assure that the Ophthalmologist spends sufficient time with each CATT patient during follow-up examinations 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.

### **14.5.3. Organization of CATT Records at the Clinical Center**

The Clinic Coordinator should set up two special loose-leaf binders at the beginning of the CATT, 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, the CATT Data System generated Treatment Assignment screen prints, and a copy of the patient contact information for each patient, in addition to the Patient Registration Logs. 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 CATT 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 CATT Study file.

Case Report Forms (CRFs) are printed directly from the Remote Data Capture System prior to a patient visit. The back-up copies provided in the CATT Forms notebook should be used only when the Data System is not functioning. Whenever CATT Study forms have been revised, the Clinic Coordinator is responsible for seeing that any old versions at the clinical

site 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 clinical site staff any changes in procedures that are required by form revisions. He/she should consult personnel at the Coordinating Center whenever there is uncertainty 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 CATT Study protocol memoranda are sent from the Coordinating Center or Chairman's office. One copy of each memorandum should be filed in numeric order in a binder 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 CATT Study staff member who is affected by the new or revised information.

#### **14.5.4. Workspace**

With so many responsibilities, it is important that the Clinic Coordinator have adequate workspace. Private office space is necessary to obtain patient histories, talking with patients and family members, making telephone calls to patients and physicians, and ensuring that patients understand the study treatment. The room should be large enough for the Clinic Coordinator's desk, file space for CATT Study 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 CATT Study Principal Investigator's office or primary examination room.

#### **14.5.5. Coordinator Activities during Follow-up Visits**

The Clinic Coordinator's activities during follow-up visits fall within 4 categories: 1) ensuring that all required procedures are conducted during the visit 2) reporting serious adverse events (if necessary), 3) submitting data to the CATT Coordinating Center, the OCT Reading Center and (if necessary) to the FPRC and 4) scheduling the next study visit.

### **14.6. CERTIFICATION OF CLINIC COORDINATORS**

All CATT Clinic Coordinators must have specific knowledge of the major eligibility criteria, treatment protocols, and procedures during follow-up visits. Protocol deviations and performance issues concerning reporting of adverse events and data submission will be monitored on a clinic and clinic coordinator-specific level. The Principal Investigator of the Clinical Site will be advised of any problems with the performance of the Clinic Coordinator in the Clinical Site.

#### **14.6.1. Specific Requirements for Clinic Coordinator Certification for CATT**

The certification process entails fulfillment of several criteria to demonstrate knowledge and proficiency in Study procedures. To be certified, the Clinical Coordinator must:

- Read specific chapters of the CATT Manual of Procedures.
- Attend a CATT Training meeting; or review of the relevant slide presentations from the training meeting.

- Complete a CATT Study General Knowledge Assessment.
- Complete a Clinic Coordinator-specific Knowledge Assessment to test knowledge of eligibility criteria, treatment protocols, follow-up schedule, and data and clinic management follow-up.
- Complete CATT database training and demonstrate proficiency with the CATT Data Management System
- Complete a telephone discussion with the Director of the Coordinating Center to assess the Coordinator's knowledge of the CATT protocol and provide an opportunity to discuss study logistics and answer any remaining questions.

A valid certification number will be issued by the Coordinating Center after the knowledge assessments have been completed, database proficiency has been demonstrated, and the telephone call has been successfully conducted.

## **14.7. CERTIFICATION OF REFRACTIONISTS**

Refractionists, along with Visual Acuity Examiners (VAEs), play a major role in obtaining the data for the primary outcome measure in CATT and must therefore have a thorough knowledge of the standard procedures for refraction. The refractionist may also be certified as the Visual Acuity Examiner. During follow-up, the Refractionist 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. The certification requirements used in CATT were adopted from the DRRCRnet. The DRRCRnet has created a "Refraction and Visual Acuity Certification Center" (RVACC) centralized website for certification of personnel performing Refraction and Visual Acuity testing in certain ophthalmologic clinical studies, including CATT. Certifications earned through this website are valid for all clinical studies participating in the centralized effort. Some of the requirements for CATT Refractionist certification will be performed via the RVACC website, as defined below.

Before CATT certification, candidates must have a basic knowledge of the principles of refraction, acquired from previous instruction or experience. All candidates for certification as a CATT Refractionist must fulfill the following requirements:

- Demonstrated familiarity with CATT rationale and procedures
- Certification in the CATT refraction protocol

### **14.7.1. Demonstrated familiarity with CATT rationale and procedures**

To become familiar with the CATT Study, candidates for Refractionist certification must fulfill the following requirements:

- Read specific chapters of the Manual of Procedures
- Complete the online CATT Study General Knowledge Assessment

## **14.7.2. Initial Refraction Certification**

### **14.7.2.1. Refraction Pre-Certification Training**

Prior to requesting certification, the individual must have experience performing refractions using the refraction protocol as detailed in Chapter 7. It is strongly encouraged that individuals requesting certification be experienced refractionists, even if not experienced with the ETDRS or similar protocol.

Prior to requesting certification, the following steps must be completed:

- 1) Read the Refraction Protocol (Chapter 7).
- 2) Perform a refraction using the protocol on both eyes of at least 10 patients.
  - At least 3 of the patients should have acuity worse than 20/100 in at least one eye.
  - If the individual is not already an experienced refractionist, the refraction should be supervised by an experienced refractionist for at least 5 of the patients.
- 3) If the individual already has experience performing refractions using this protocol (or a nearly identical one), this experience may be counted toward fulfilling the 10 patient requirement.

### **14.7.2.2. Submitting Refractionist Certification Request**

The steps involved in the initial certification process include the following:

- 1) Complete the necessary pre-certification training described above
- 2) Submit the Initial Refraction Certification Request Form on the RVACC website
- 3) Upon submission of form, an email is sent to a Refraction Certification Examiner
- 4) The Examiner will contact the candidate requesting certification within 1-2 business days via phone or email to schedule a time for an Initial Phone Call.

## **14.7.3. Refraction Phone Certification Procedures**

### **14.7.3.1. Initial Phone Call or Email**

In this contact, the Certification Examiner (1) will confirm that the candidate has completed all of the steps necessary prior to certification testing and (2) will ask the candidate questions about the procedure to ascertain that the candidate is prepared for the formal testing. Assuming that the candidate and the Certification Examiner agree to proceed, an appointment will be scheduled for the formal certification procedure.

### 14.7.3.2. Certification Phone Call

For the formal certification teleconference, the candidate will need to be in an exam room with the following items:

- A speaker phone is preferred for “hands-free” work.
- If a phoropter will be used, one should be present.
- If the refraction will be done manually using a trial frame (preferred), then trial frames, proper Jackson cross cylinders, and a complete lens set is necessary.
- EVEN IF A PHOROPTER WILL BE USED THE CANDIDATE **MUST** HAVE TRIAL FRAMES AND A COMPLETE LENS SET AVAILABLE TO DEMONSTRATE THE ABILITY TO PROPERLY PLACE THE OBTAINED RERACTION IN THE TRIAL FRAMES.
- A copy of the EVA Refraction Testing form (Exhibit 14-1). Alternatively, the ETDRS Chart R (Exhibit 7-2) can be used, however, the EVA Refraction Testing form must still be available for recording refraction.

During the phone certification, the Certification Examiner will act as a patient.

The Examiner will provide a starting refraction that the candidate will place in trial frames/phoropter and then the refraction will proceed just as if the Examiner was sitting in the chair in front of the candidate. The refraction must be properly put in the trial frames if a phoropter is used.

### 14.7.4. Recording of Results

Upon completion of the certification testing, the Examiner determines if the candidate has passed.

- The Examiner then accesses the RVACC website and records the results.
- The Refractionist and the CATT Coordinating Center are notified of results via auto email.

### 14.7.5. Maintaining Active Certification

To maintain active certification, a refraction exam must be done on a patient in a RVACC participating study at least once every 4 months. If a Refractionist does not perform refraction within the 4 month period, then her/his certification status will be changed to inactive. Individuals with inactive status will need to undergo the full certification procedure for active status to be restored.

Should a lapse in certification occur, the Refractionist will need to complete the Annual Refraction Re-certification Request Form located on the RVACC website. Once this form is completed, a Certification Examiner will contact the Refractionist to schedule a certification teleconference. Upon completion of the certification teleconference, the Refractionist will be assigned a grade of either passing or failing, which the Examiner will report on the RVACC



website. Once the grade has been entered, an email will be sent to the Refractionist, and the Coordinating Center.

#### **14.7.6. Annual Refractionist Re-Certification**

Annual refraction re-certification **MUST** be completed once every 12 months with the same phone certification process described above, regardless of current certification status. Emails will be sent on a monthly basis from the Coordinating Center to the clinical centers detailing which Refractionist's certification will expire within the next 30 days.

To request re-certification, the Refractionist must complete the Refraction Re-certification Request Form located on the RVACC website. Upon submission of the refraction recertification test online, a Certification Examiner will schedule a recertification teleconference with the Refractionist. The certification status will be renewed once the recertification call has been completed.

### **14.8. CERTIFICATION OF VISUAL ACUITY EXAMINERS**

Visual Acuity Examiners (VAEs) play a major role in obtaining the data for the primary outcome measure in CATT and must therefore have a thorough knowledge of the standard procedures for Visual Acuity testing. The VAE may also be certified as the Refractionist. During follow-up, the VAE 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. The certification requirements used in CATT were adopted from the DRCRnet. The DRCRnet has created a "Refraction and Visual Acuity Certification Center" (RVACC) centralized website for certification of personnel performing Refraction and Visual Acuity testing in certain ophthalmologic clinical studies, including CATT. Certifications earned through this website are valid for all clinical studies participating in the centralized effort. Some of the requirements for CATT Visual Acuity Examiner certification will be performed via the RVACC website, as defined below.

All candidates for certification as a CATT Visual Acuity Examiner must fulfill the following requirements:

- Demonstrated familiarity with CATT rationale and procedures
- Certification in the CATT visual acuity protocol

#### **14.8.1. Demonstrated familiarity with CATT rationale and procedures**

To become familiar with the CATT Study, candidates for VAE certification must:

- Read specific chapters of the Manual of Procedures
- Complete the online CATT Study General Knowledge Assessment

#### **14.8.2. Certification for Visual Acuity Testing Using the Electronic Visual Acuity Tester (EVA) and ETDRS charts**

### **14.8.2.1. Procedures for Initial VAE Certification**

The following steps should be completed:

- 1) Read the Visual Acuity Testing Procedures in Chapter 7 of this Manual regarding:
  - a. Electronic Visual Acuity Tester and its calibration
  - b. E-ETDRS Testing Protocol
  - c. Standard ETDRS Visual Acuity Protocol
- 2) Check the EVA calibration
- 3) Perform visual acuity testing using the E-ETDRS testing protocol separately on each eye of one individual
- 4) Complete the Visual Acuity Initial Certification Request form on the RVACC website.

### **14.8.3. Maintaining Active VAE Certification**

In order to maintain active certification, a visual acuity test must be performed at least once every six months on the EVA or the ETDRS chart (if the EVA is not functioning). Emails will be sent on a monthly basis from the Coordinating Center to the clinical centers detailing which Visual Acuity Examiner's certification will expire within the next 30 days.

Should a lapse in certification occur (i.e. a VA test not performed within 6 months), the VA Examiner will become inactive and will need to complete the EVA Visual Testing Re-Certification Request Form located on the RVACC website. If the VAE passes the online certification test, their status will be returned to active. Should the VA tester fail the online certification test, a teleconference with a Certification Examiner must be completed before their active status can be reinstated.

### **14.8.4. Annual Visual Acuity Examiner Re-Certification**

Visual Acuity Examiner certification must be renewed once every 12 months with a process similar to the process described above for the initial certification. To recertify, the VAE must complete the Visual Acuity Re-certification Request Form on the RVACC website. If the VAE passes the online certification test, their certification will be renewed. Should the VA tester fail the online re-certification test, a teleconference with a Certification Examiner must be completed before their certification status can be renewed.

## **14.9. CERTIFICATION OF OCT TECHNICIANS**

To be certified, OCT technicians must be able to consistently obtain high-quality OCT images so that the clinical center CATT ophthalmologist can make appropriate decisions regarding patient study eligibility, and need for re-treatment. In addition, high quality images are essential so that the OCT Reading Center can provide accurate OCT scan grading data that will be correlated with information obtained by clinical examination, visual acuity testing, fundus photography, and fluorescein angiography. The OCT technician must also demonstrate the ability to accurately transmit electronically the OCT scan data and accompanying study identification information to the OCT Reading Center, so that it can be properly interpreted,

and archived. The OCT Technician must be certified by the OCT Reading Center for OCT study procedures prior to obtaining study patient OCT scans and transmitting them to the OCT Reading Center. Only a CATT-certified OCT technician is permitted to obtain OCT scans for initial study visits.

To become certified for the Study, **all** OCT Technicians must perform the following:

- Read specific chapters of the Study Manual of Procedures
- Complete the on-line CATT Study General Knowledge Assessment
- Complete the on-line OCT Technician Knowledge Assessment

In addition, OCT Technicians **previously certified** by the OCT Reading Center for submitting OCT scans **online** are required to Submit the Request for OCT Certification Based on prior Certification Form.

In addition, OCT Technicians **previously certified** by the OCT Reading Center for submitting OCT scans **by CD** are required to submit one OCT image via the web-based Data Transmission Site (DTS) following the procedures in Chapter 9.

**New** OCT Technicians must read Chapter 9 and create protocol scans on the Stratus OCT for certification according to the procedures presented in Chapter 9.

#### 14.9.1. Required OCT Scans for Certification

Scans from two patients are required. At least one eye of each patient must have macular pathology. The OCT scans must be labeled and submitted electronically via DTS according to the Study OCT scan protocol (see Chapter 9 Procedures for OCT, Section 9.4, Certification for CATT for details).

The specific scans to be performed on each eye include:

- 2 separate **Fast Macular Thickness Map (FMTM)** scan groups producing 2 distinct “Retinal Maps” of each eye
- 2 custom horizontal **7mm Posterior Pole** scans
- 2 vertical **6mm Posterior Pole** scans

Summary of 24 certification scans of 2 patients:

4 FMTMs per patient:	8 Total
4 7 mm Posterior Pole scans per patient:	8 Total
4 6 mm Posterior Pole scans per patient:	8 Total

All scans must be de-identified by established HIPAA guidelines. No identifiable patient data should be present on any material submitted, not limited to name, medical record number, birthday, etc. A Transmittal Log should also be completed, listing the sets of submitted OCT scans.

The Senior Technical Analyst or Technical Analyst will review the OCT scans and makes one of the following judgments:

- The OCT scan images are acceptable and OCT Technician certification is granted once the knowledge assessment has been completed, and the OCT technician has confirmed in writing that he/she has read the applicable Manual of Procedures Chapters;
- The quality of the scans is marginally acceptable or unacceptable and improvement is necessary. In this case, the Senior Technical Analyst contacts the technician and discusses the deficiencies. Another set of scans must be submitted and evaluated as acceptable before certification can be granted.

#### **14.9.2. Read Specific Chapters CATT Manual of Operations**

To be familiar with the study design and procedures, OCT technicians are required to read the following chapters of the CATT Manual of Procedures: Chapters 1 through 5, 9, 12 through 14 and 18.

### **14.10. RESPONSIBILITIES OF THE CATT FUNDUS PHOTOGRAPHERS**

The fundus photographer is responsible for:

- Completing the requirements to certify the digital imaging system (Chapter 8, Section 8.2),
- Obtaining the fundus photographs and fluorescein angiograms,
- Downloading images to CDs for submission to the FPRC, and
- Maintaining the digital imaging system certification during the course of the study.

#### **14.10.1. CERTIFICATION OF PHOTOGRAPHERS**

Photographers must demonstrate their ability to consistently obtain good quality stereo photographs and stereo angiograms so that the Photograph Reading Center can determine patient eligibility with confidence and determine the status of the neovascular AMD lesion at baseline and during follow-up. The photographer must also demonstrate the ability to download digital images and submit the images to the Fundus Photograph Reading Center to confirm that the digital imaging system conforms to study specifications and that the images submitted can be accessed at the FPRC. The photographers are required to demonstrate their general understanding of the CATT study procedures on the knowledge assessment forms as well as to demonstrate their proficiency in performing the CATT photography protocol.

If a Clinical Center is certified for film photography rather than digital or if the Clinical Center's digital system does not meet the study criteria (See Chapter 8, Procedures for Fundus Photography), the requirements for the photographer certification are the same as for digital certification, except film will be submitted.

#### **14.10.2. Digital Angiography and Film Color Photography**

If the Clinical Center's digital imaging system meets the criteria for fluorescein angiography but does not meet the standards for color digital images, a Clinical Center can be certified to submit color film images and digital fluorescein angiograms. The photographer will need to

submit photographs for certification in the format for which his/her Clinical Center is certified. **A Clinical Center cannot be certified to submit color digital images and film fluorescein angiograms.**

Upon successful completion of all certification requirements, a certification number for each photographer and digital imaging system will be issued by the Coordinating Center.

### **14.10.3. Specific Requirements for Photographer Certification for CATT**

Photographers must be certified by the Fundus Photograph Reading Center for study procedures prior to photographing and submitting photographs of study patients. Only study certified photographers are permitted to take photographs for initial study visits.

To be certified a study photographer is required to:

- Submit acceptable quality stereo color photographs and stereo fluorescein angiograms acquired on a CATT certified imaging system (Section 14.13.3);
- Read specific chapters of CATT Manual of Procedures;
- Complete the online CATT Study General Knowledge Assessment
- Complete the online CATT Photographer Knowledge Assessment;

#### **14.10.3.1. Submission of Photographs for Certification**

Photographers may submit images for certification purposes only after the imaging system is certified by the CATT FPRC. Each photographer is required to submit color photographs and fluorescein angiograms of four patients with AMD taken according to the CATT protocol (see Chapter 8, Procedures for Fundus Photography). These four patients would have had an angiogram performed for management of their condition, not just for photographer certification purposes. The color photographs and angiogram of an individual patient must be taken on the same day. The four patients must be photographed within a 4-week period.

The photographs and angiograms must be labeled and submitted to the FPRC according to the procedures detailed in Chapter 8, Procedures for Fundus Photography. The patient's name must not appear on the photographs or angiograms. The materials for certification must include a completed Photograph Inventory Form for each patient. A Photographer Certification Submission of Images for Review Form should be completed also, listing the four sets of submitted images.

A senior photograph reader reviews the color photographs and angiograms and makes one of the following judgments:

- The photographs are acceptable and photographer certification is granted;
- The quality of the photographs is marginally acceptable or inconsistent and improvement is necessary. In this case, the senior reader contacts the photographer and discusses the deficiencies. Another two sets of photographs

must be submitted and evaluated as acceptable before certification can be granted.

#### **14.10.3.2. Read Specific Chapters CATT Manual of Procedures**

To be familiar with the study design and procedures, photographers are required to read the following chapters of the CATT Manual of Procedures: Chapters 1 through 5, 8, 12 through 14 (Certification Requirements for CATT Photographers) and 17.

#### **14.10.3.3. Waiver for Photographer Certification for Digital Images**

Digital Fluorescein Angiography: If a photographer is certified by the University of Wisconsin-Madison Fundus Photograph Reading Center (UW FPRC) for another study that is using the UW FPRC Digital Fluorescein Angiography protocol, the photographer may be granted a waiver for the submission of fluorescein angiography. A photographer qualifies for a waiver if 75% of his/her angiograms taken within the last 365 days were graded as Fair and no more than 10% of the photographs were graded as Poor. Documentation of the certification and the quality of the images will be required from the UW FPRC.

Digital Color Images: A waiver based on documentation from the UW FPRC reduces the number of sets of digital color photographs to be submitted from four to two. This is necessary to document the quality of the digital color images that are not required by the UW FPRC. The waiver does not change the requirement to complete the knowledge assessment forms. A waiver will be granted once the prior certification is confirmed and the color digital images submitted are evaluated as acceptable.

Provisional Status with Waiver Granted: When a waiver is granted for digital images, provisional status will be established. The first five digital angiograms submitted will be reviewed for quality and completeness. If the quality is acceptable, full certification will be granted. This will ensure that the photographer is currently obtaining acceptable quality images for CATT.

#### **14.10.3.4. Waiver for Photographer Certification for Film Images**

If a photographer is certified by the University of Wisconsin-Madison Fundus Photograph Reading Center (UW FPRC) for another study that is using the UW FPRC Fluorescein Angiography protocol, the photographer may be granted a waiver. The waiver reduces the number of sets photographs (angiogram and colors photos) to be submitted from four to one. A photographer qualifies for a waiver if 75% of his/her angiograms taken within the last 365 days were graded as Fair and no more than 10% of the photographs were graded as Poor. Documentation of the certification and the quality of the images will be required from the UW FPRC. The waiver does not change the requirement to complete the knowledge assessment forms. A waiver will be granted once the prior certification is confirmed and the color photographs and angiogram are submitted to the CATT FPRC and are evaluated as acceptable.

Provisional Status with Waiver Granted: When a waiver is granted for film images, provisional status will be established. The first five sets of photographs submitted will be reviewed for quality and completeness. If the quality is acceptable, full certification will be granted. This will ensure that the photographer is currently obtaining acceptable quality images for CATT.

## **14.11. CERTIFICATION NUMBERS**

The Coordinating Center will maintain a log of certification numbers. Each person will have one CATT 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 at the Coordinating Center 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.

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

In addition to the individual role specific certifications, the Coordinating Center will also certify the clinical sites. The Clinic Coordinator at each site is responsible for completing the online CATT Site Certification Checklist. The checklist identifies the requirements to be completed at each clinical site before patient recruitment can be initiated at the site. Application for and receipt of Institutional Review Board approval of the clinical trial, acquisition of the testing equipment required for the CATT protocol, appropriate facilities to store study medications, verification that examination rooms have the required lighting levels and testing distances, receipt of the required Study documents, 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 CATT protocol available on the days that CATT patients are scheduled for clinic visits to the site.

### **14.12.1. Refraction and Visual Acuity Equipment Certification**

Sites must have the appropriate Visual Acuity and Refraction Equipment at each location where patients are seen,

#### **14.12.1.1. Electronic Visual Acuity Tester (EVA)**

All sites that do not have an EVA available will receive one for use for the CATT. Upon receipt, the EVA Calibration Form is completed (see Section 7.5.2 for calibration instructions) and sent to the Coordinating Center.

#### **14.12.1.2. ETDRS Charts**

For back-up purposes, sites should have ETDRS charts to use if the EVA is not operational (and there is only one EVA at the site). **Note: Standard ETDRS equipment will ONLY be used as a back up if the Electronic Visual Acuity Tester (EVA) is not operational.**

#### **14.12.1.3. Trial Frames and Complete Lens Set**

For refraction, either trial frames or a phoropter can be used. For visual acuity testing, trial frames are used.

### **14.12.2. Specific Requirements for OCT Machines**

The Stratus OCT machine (Zeiss-Meditec, Dublin, CA) with Stratus Software version 4.0 or higher will be used in CATT. No other equipment is permitted at this time. It is likely that

new hardware and software will become available during the conduct of CATT. This new hardware and software will be evaluated on an ongoing basis by the OCT Reading Center for possible use by CATT clinical centers.

### **14.12.3. Specific Requirements for Digital Image Systems**

Because of the variability among manufacturers of digital imaging systems, each system must meet specific criteria to be certified for CATT prior to enrolling patients. Each imaging system to be used for CATT must be certified by the CATT FPRC prior to the photographer submitting images for certification to the CATT FPRC. The process for the certification of the digital imaging systems is detailed in Chapter 8, Procedures for Fundus Photography. If a clinical center is unable to meet the digital imaging system requirements, it can be certified for film-based photography. A clinical center will be certified for either film angiography or digital angiography but not both. A certification number will be issued for each digital system certified.

### **14.13. MAINTAINING CERTIFICATION**

Each year, the Clinic Coordinator will be responsible for verifying that the equipment and space required for CATT are still available at each certified site. The availability of a full CATT team at each site when CATT 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 CATT protocol. Performance at the clinical center, site, and person level will be reviewed. The Coordinating Center Director and other committee members will be responsible for developing a plan to resolve any performance problem detected. If CATT 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.



**EXHIBIT 14-1**  
**CERTIFICATION WORKSHEET**  
**CATT – EVA REFRACTION TESTING FORM**

*EVA Refraction Chart*

20/800	R O K C S
20/640	N D C K H
20/500	V H D O S
20/400	N R Z V Z
20/320	S O V N D
20/250	O D N V Z
20/200	R H R C K
20/160	C S H K H
20/125	D C V O S
20/100	N K Z R C
20/80	S O R Z V
20/63	N K C V H
20/50	S H K N R
20/40	Z D O D C
20/32	R O V H S
20/25	O S H K C
20/20	R N D Z V
20/16	Z D N K O
20/12	K N V Z S

**Refraction:**

**OD** \_\_\_\_\_ @ \_\_\_\_\_ °

**OS** \_\_\_\_\_ @ \_\_\_\_\_ °

\_\_\_\_\_  
Name of Person Performing Refraction

\_\_\_\_\_  
Signature of Person Performing Refraction

\_\_\_\_ / \_\_\_\_ / 20 \_\_\_\_  
Date (MM/DD/20YY)

## CHAPTER 15

### OPERATIONS AND PROCEDURES OF THE STUDY CHAIRMAN'S OFFICE

#### 15.1 Responsibilities of Study Chairman

The Chairman is responsible for the overall conduct of the Study throughout all phases of the study. To facilitate discussion, the responsibilities of the CATT Study Chairman's Office 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 trial.

##### 15.1.1 Initial Design Phase and Protocol Development

During the initial design phase of the trial, the Study Chairman plays a major role in the following activities:

- Developing the study design with the Planning Committee and Coordinating Center;
- Developing the guidelines for retreatment with study drugs;
- Determining eligibility and examination criteria for entry and exclusion to the trial in collaboration with the CATT Operations Committee;
- Outlining examination, testing, and safety procedures;
- Determining primary and secondary outcomes;
- Actively participating in the selection of CATT Clinical Centers;
- Developing procedures for training and certifying CATT ophthalmologists at each clinical center;
- Refining and editing chapters of the *Manual of Procedures*;

##### 15.1.2 Final Preparation for the Initiation of the Trial

Prior to initiating the Study, a number of activities will be performed by the Chairman to begin the trial with a fully developed protocol. These activities include:

- Finalize the protocol details;
- Review all case report forms;
- Review plans for grading images by the OCT and Photograph Reading Centers;
- Establish agenda for training meetings for key CATT clinical staff;
- Review patient consent and human subject considerations for local IRB submission;
- Participate in the development of and review of patient recruitment materials including patient information brochures, brochures for referring ophthalmologists, and design slides for presentation by CATT ophthalmologists at local professional meetings;
- Participate in a meeting of the Data and Safety Monitoring Committee to review the protocol.

### 15.1.3 Patient Recruitment and Treatment and Follow-up Phase

Activities during this phase can generally be categorized as administrative, problem management, data interpretation and presentation, and planning for future trials. The Study Chairman's responsibilities are summarized for each category.

#### *Study Administration*

- Participate in the affairs of each of the standing committees, chairing the Operations and Executive Committees;
- Participate in planning and lead the annual Investigative Group meeting;
- Participate in open sessions of the Data and Safety Monitoring Committee (DSMC);
- Serve as the primary source on questions arising concerning ophthalmologic eligibility criteria and patient care;
- Serve as the spokesperson for public relations about the Study beyond local scope, delegating activities to others within the study group deemed appropriate;

#### *Problem management*

- Regularly address recruitment issues with the principal investigator and staff at clinical centers;
- Discuss the treatment protocol with study ophthalmologists who make retreatment decision inconsistent with the trial guidelines;
- Address safety issues that arise during the trials;
- Address poor follow up at clinic centers;
- Travel to clinic centers having problems with study performance with the site visitors from the Coordinating Center;

#### *Data interpretation and presentation*

- Participate in drafting all primary study publications;
- Establish writing committees for all study publications;
- Reporting the primary results of the study to appropriate audiences.

#### *Planning for future trials*

- Keep abreast of scientific developments and industry efforts in the area of new treatments for choroidal neovascularization;
- Develop, in conjunction with the Executive Committee, the research design for additional clinical trials for neovascular age-related macular degeneration;

#### 15.1.4 Patient Closeout Phase

- Help develop a plan for subsequent care of patients completing the study;
- Inform all principal investigators of clinical centers of the requirements for storage and retention of study documents and patient records to be in compliance with NIH, FDA, IRB, and HIPAA guidelines.

#### 15.1.5 Termination Phase

- Develop and maintain a plan for sharing of CATT data;;
- Disseminate CATT results to medical and news organizations and the public.

### 15.2 Organization of the Study Headquarters

#### 15.2.1 Internal Organization

The staffing of the Office of the Study Chairman includes the following:

- Chairman (Principal Investigator)
- Vice-Chairman
- Administrative Assistant

#### 15.2.2 Personnel Responsibilities

The responsibilities of the Chairman have been described above in detail. Responsibilities of the other members of the Office of the Study Chairman follow:

The **Vice-Chairman** will have responsibility both for specific areas of activity and for providing general advice to the Chairman and Executive Committee on administration of multicenter clinical trials. These responsibilities include:

- Contacting investigators at CATT centers to discuss problems with recruitment or reinforcing successful recruitment of study patients;
- Participating as a member of the Executive Committee;
- Advising the Chairman and Executive Committee on specific areas such as maintaining active participation of clinical centers and management of performance problems in clinical centers,
- Taking on the lead role for specific tasks, as designated by the Chairman;

The **Administrative Assistant** will provide secretarial and administrative support to the Study Chairman and Vice-Chairman. Specific responsibilities include:

- To maintain an up-to-date study resource materials for the Office of the Study Chairman in both printed and electronic form including the study telephone, address, FAX, and e-

mail directory (distributed by the Coordinating Center), *Manual of Procedures*; protocol memoranda, recruitment materials, and materials provided in support of study meetings;

- To prepare documents written by the Study Chairman and transfer them to the Coordinating Center for distribution or directly to specific CATT committees;
- To monitor grant expenditures and prepare materials for the annual non-competing grant continuations;
- To make travel arrangements;
- To maintain office supplies,
- To assist the Chairman and Vice Chairman as necessary to meet the needs of the Study.

## CHAPTER 16

### COORDINATING CENTER OPERATIONS AND PROCEDURES

#### 16.1. Responsibilities of the Coordinating Center

The Coordinating Center's responsibilities are varied and change as the study progresses. To facilitate discussion, the responsibilities of the CATT Coordinating Center are organized according to the 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 trial.

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

During the initial design phase of the trial, the Coordinating Center staff plays 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;
- Drafting chapters of the *Manual of Procedures*;
- Submitting materials to the FDA for an IND
- Outlining the data collection forms;
- Planning the design of a World Wide Web-based data capture system;
- Developing a web-based certification system for staff at CATT Clinical Centers
- Outlining data management procedures, including the division of labor and responsibility between data management staff within the Center for Preventive Ophthalmology and Biostatistics (CPOB) and staff within the Clinical Research Computing Unit (CRCU);
- Collaborating with and coordinating all activities of the Clinic Selection Committee including establishing requirements for, recruiting, and ascertaining the patient recruitment potential of the clinical centers and organizing the selection process.
- Selecting an Investigational Drug Distribution Service;
- Collaborating with the Investigational Drug Distribution Service in developing plans for drug repackaging, distribution and destruction;
- Implementing communication plans between the Coordinating Center, CRCU, Drug Distribution Service, OCT Reading Center, the Photograph Reading Center and the Study Chairman's Office;
- Initiating the Purchased Services Agreements with CATT clinical centers;

- Developing procedures to report serious adverse events;
- Developing quality assurance procedures for all aspects of the CATT.

### **16.1.2. Final Preparation for the Initiation of the Trial**

Prior to initiating the Study, a number of activities will be 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 the study. These activities include:

- Finalizing protocol details;
- Drafting, pilot testing, and finalizing the data collection forms;
- Generating treatment allocation schedules for patients;
- Providing the CRCU with treatment allocation schedules for incorporation into the randomization process;
- Finalizing the data collection and data management system to integrate all Study activities including OCT and photograph grading data;
- Preparing other materials to be used by clinical center staff, such as patient logs and other auxiliary forms;
- Completing beta testing of the web-based CATT data system for baseline forms and the randomization module;
- Completing beta testing of the web-based CATT data system with follow-up visit forms;
- Completing beta testing of the web-based adverse event reporting system;
- Completing beta testing of the web-based clinic staff certification system;
- Organizing the agenda for orienting, training, and certification of clinic staff at a kickoff Investigative Group training meeting;
- Developing the patient consent and IRB protocol for local IRB submission;
- Training and certifying CATT Clinic Coordinators and Visual Acuity Examiners;
- Distributing the *Manual of Procedures* and Address Registry to all clinical centers;
- Supplying each clinical center with a set of study data collection form masters;
- Developing and distributing Power Point presentations for clinical center use to address local physician groups for enrollment;
- Drafting a study patient information brochure to enhance recruitment.
- Preparing a pocket card listing key eligibility criteria for participating ophthalmologists;

- Developing a newsletter for clinic staff to enhance communication and study recruitment;
- Establishing an electronic and paper repository for CATT study documents, such as minutes, manuals, etc.;
- Ensuring that each clinical site has the required equipment and study drugs;
- Establishing clear communications between the Coordinating Center and the Drug Distribution Service at the University of Pennsylvania;
- Establishing clear communications between the clinical centers and all CATT resource centers (Coordinating, OCT Reading, Fundus Photograph Reading, and Drug Distribution Centers);
- Participating in a meeting of the Data and Safety Monitoring Committee to review the protocol;
- Developing and implementing procedures for certifying CATT clinical centers;
- Finalizing procedures for site visits to clinical centers;
- Initiating site visits by Protocol Monitors;
- Collaborating with the OCT Reading Center and Photograph Reading Center to finalize the quality control program for image grading;
- Developing an informational study website for use by CATT personnel at the clinical centers and resource centers;
- Preparing and distributing minutes of meetings;
- Establishing and maintaining an electronic roster of certified study personnel.

### **16.1.3. Patient Recruitment and Enrollment, Treatment and Follow-up Phase**

Activities during this phase can generally be categorized as administrative, data collection and management, 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 materials in support of all study meetings;
- Coordinating communications among the various functional units and committees;
- Assisting the staff of each clinical center to interpret and follow the protocol and procedures documented in the *Manual of Procedures*;
- Managing the Purchased Services Agreements with clinical centers;



- Supplying the clinical centers with new and revised data collection forms, template consent forms and other printed materials;
- Maintaining accurate study archives, including study history and proceedings of committee meetings;
- Preparing and distributing to clinical centers reminders of upcoming patient visits and materials overdue;
- Coordinating the annual meetings of the Investigative Group in collaboration with the Office of the Study Chair.
- Maintaining an accurate CATT telephone, address, fax, and e-mail directory;
- Publishing and distributing study newsletters for patients and clinical center staff;
- Developing and implementing an informational study website for study patients.

#### *Data Collection and Management*

- Receiving data electronically submitted from the clinical centers via the web-based data capture system;
- Assisting clinical center staff with patients for whom follow-up is a problem;
- Receiving and maintaining SAS datasets of all data records created by the graders at the OCT Reading Center and Photograph Reading Center;
- Providing on-going support and reference to the Clinic Coordinators regarding data collection and adverse event reporting procedures;
- Performing edit checks to ensure high quality data.

#### *Data Analysis and Reporting*

- Preparing reports for the Investigative Group concerning the status of patient recruitment, patient follow-up, and adherence to the protocol;
- Preparing study-wide adverse event reports for the CATT Medical Safety Monitor and FDA;
- Preparing periodic reports for the Data and Safety Monitoring Committee concerning adverse and beneficial treatment effects;
- Preparing and submitting all reports needed to meet FDA requirements associated with operating under an IND;
- Preparing tables and summaries of compliance of CATT ophthalmologists with the study retreatment guidelines for review by the Treatment Monitoring Committee;
- Developing analytic methods appropriate to the study design, in conjunction with the Data and Safety Monitoring Committee;
- Preparing all analyses to be reported in publications from the study;

- Participating in the drafting of all study 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 study design if these appear to be necessary;
- Reporting to appropriate audiences statistical and methodological innovations developed during the course of the study.

#### *Quality Assurance*

- Conducting initial training sessions for clinic personnel to review study design, data collection methods, adverse event reporting, and procedures for interfacing with the Drug Distribution Service, the OCT Reading Center, the Fundus Photograph Reading Center, and the Coordinating Center;
- Visiting each clinical center to review procedures, verify data entered from source medical records, and to “troubleshoot” in any area in which the clinical site may require it;
- Preparing monthly reports summarizing patient recruitment in each clinical site,
- Preparing quarterly reports on data quality and protocol adherence in the clinical centers for the Clinic Monitoring Committee and the Treatment Monitoring Committee;
- Maintaining documentation of all procedures and operations at the Coordinating Center;
- Maintaining the data files in a secure manner to assure their integrity and adherence with HIPAA requirements;
- 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;
- Cooperating with any individual or group assigned to review operations at the Coordinating Center.

#### *Planning for Future Phases*

- Maintaining an up-to-date summary of the development status of alternative treatments for neovascular AMD, with particular emphasis on candidates for combination therapy;
- Developing procedures for closing out patient follow-up at the appropriate time;
- Implementing a data sharing plan consistent with NIH guidelines;
- Planning for permanent, accessible storage of study records and data.

#### **16.1.4. Patient Closeout Phase**

As with earlier phases of the study, the primary responsibilities of the Coordinating Center staff during the Patient Closeout phase are centered on coordination, developing, testing, and refining procedures, and data management 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 as specified by NIH, FDA, and local IRB, HIPAA, and institutional guidelines;
- Developing plans for final data editing and storage;
- Completing plans for final analysis and preparation of publications;
- Participating in paper writing activities;
- Providing a mechanism for continuing communications among investigators and performing additional analyses;
- Monitoring of archiving of images and destruction of excess study medication.

#### **16.1.5. Termination Phase**

During the last phase of the study, communications with the investigators at the clinical centers will continue to be important. The Coordinating Center anticipates engaging in the following activities during this period:

- Completing scheduled data analyses;
- Placing data files, documentation, and other materials in the selected archives;
- Distributing draft manuscripts and reprints of publications to the other investigators;
- Preparing Power Point presentations summarizing results from publications for use by CATT investigators;
- Serving as the communications center for the study.

### **16.2. Organization of the Coordinating Center**

#### **16.2.1. Internal Organization**

Staffing at the Coordinating Center may change as the study progresses. The staffing of the Coordinating Center includes the following roles as organized in Exhibit 16-1:

- Principal Investigator
- Director
- Protocol Monitor(s)
- Systems Analyst
- Data Assistant
- Office Manager
- Senior Biostatistician
- Junior Biostatistician
- CRCU Technical Director
- Financial Administrator

### **16.2.2. Personnel Responsibilities**

The Coordinating Center **Principal Investigator** has responsibility for providing leadership and guidance to the study in areas related to study design, administration, and implementation. The Principal Investigator also has overall responsibility for all functions of the Coordinating Center and works closely with the Director to determine the general approach and methods to be used in each area of Coordinating Center operations. Specific responsibilities include:

- To serve as a voting member of the CATT Operations Committee with responsibility for developing the agenda for each meeting in consultation with the CATT Study Chairman;
- To serve as a voting member of the CATT Executive Committee with responsibility for developing the agenda for each meeting in consultation with the CATT Study Chairman;
- To organize and plan for meetings for the Investigative Group, in collaboration with the CATT Chair;
- To lead internal meetings of the Coordinating Center staff;
- To provide advice and guidance to the Coordinating Center staff on methods consistent with the standards of good practice for multi-center clinical trials.
- To consult with the Systems Analyst, CRCU Technical Director, and Biostatisticians in the refinement of the data management system and development of new subsystems;
- To work with the Biostatisticians to design analyses of the study data for treatment monitoring and performance monitoring;
- To collaborate with the other study investigators to prepare study findings for publication;

- To assist with planning and preparation of Data and Safety Monitoring Reports;
- To serve as a resource in problem solving for the clinical centers;
- To identify and summarize emerging information on treatments for neovascular AMD as available from journal articles, press releases, presentations at professional meetings, etc.;
- To work with the Financial Administrator on the budgetary matters for the Coordinating Center and the business arrangements with the drug distribution center;
- To administer, with the Financial Administrator, the Purchased Services Agreement with the Clinical Centers and administering the payment plan for patient care costs

The **Director** is responsible for the daily operations of the the Coordinating Center. Specific responsibilities include:

- To have a thorough knowledge of the study 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 CATT Operations Committee;
- To serve as a non-voting member on the CATT Executive Committee;
- To serve as chair of the CATT Clinic Monitoring Committee;
- To serve as chair of the Data Forms Development Committee;
- To develop new data collection forms, in consultation with the Data Form Development Committee;
- To supervise quality assurance activities at the Coordinating Center and clinical centers with input from the Principal Investigator;
- To oversee the certification process including implementation of the web-based knowledge assessment system for all study staff;
- To supervise the day-to-day Coordinating Center activities in the areas of data collection, data management, data reporting, data analysis, quality assurance and administrative support activities;
- To develop, in association with the Principal Investigator, the Coordinating Center budget for annual continuation applications;
- To develop annual progress reports for the NEI;
- To prepare correspondence and progress reports for the Penn IRB;
- To coordinate activities for staff recruitment with the university personnel office;
- To perform some site visits to the clinical centers, as needed 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 Study *Manual of Procedures*
- To critically review all interim reports for consistency and accuracy;
- To supervise the production of the periodic reports required by the Data and Safety Monitoring Committee, Investigative Group, Clinic Monitoring Committee, and Treatment Monitoring Committee;
- To supervise the development of an informational study web site for the Investigative Group and study patients;
- To plan and present the initial training for all CATT Clinic Coordinators;
- To collaborate with other CATT investigators to prepare Study findings for publication.

The **Protocol Monitor**, in conjunction with the Director, is the first line contact with clinical center staff with regard to issues of certification and questions concerning study protocol and good clinical research practices. Because of the Monitor's thorough knowledge of CATT procedures and close contact with clinical staff, the Director will delegate all or portions of specific projects to the Protocol Monitor. The Protocol Monitor is also responsible for supervising the CATT Site Visitors. Specific responsibilities include:

- To provide telephone support to clinical center staff with questions regarding the study protocol and to refer appropriate questions to the Principal Investigator or Director of the Coordinating Center, the Directors of the OCT Reading Center, Fundus Photograph Reading Center, the Drug Distribution Service, the Study Chairman, or the Executive Committee;
- To keep in touch with the staff at each clinical site through quarterly telephone interviews with each Clinic Coordinator and to bring areas of concern to the attention of the Director and/or Clinic Monitoring Committee;
- To oversee the certification and re-certification of the Visual Acuity Examiners and Refractionists, in collaboration with the AREDS2, SCORE and DRCRNet certification programs;
- To serve on the Data Form Development Committee;
- To serve on the Clinic Monitoring Committee;
- To schedule and conduct site visits to all clinical sites or assign visit to another Site Visitor.
- To query clinical center staff about missing and delinquent data
- To oversee the production of the study newsletters for patients and clinic staff;
- To develop new data collection forms, in consultation with the Data Form Development Committee;

- To maintain the database on study certified personnel;
- To follow-up on identified problems until they are resolved;

Because the Coordinating Center serves as the data reporting and analysis arm of the study, data management staff members are crucial to the successful operation of the Coordinating Center. Data management is a collaborative effort among staff of the Center for Preventive Ophthalmology and Biostatistics (CPOB) and the Clinical Research Computing Unit (CRCU) of the University of Pennsylvania. Specific responsibilities of the CPOB **Systems Analyst** are:

- To collaborate with the CRCU Technical Director on the overall design of the CATT data management system, taking the lead role in the specifications and project management aspects while the CRCU Technical Director leads on the development and deployment of the web-based data capture system.
- To generate randomization schedules for the clinical centers and provide the CRCU with a file of the randomization schedules to be incorporated into the randomization process;
- To develop documentation for users of the study SAS datasets;
- To develop an internal SAE monitoring database;
- To develop and maintain a quality control and reporting system that meets the needs of the study;
- To serve on the Data Form Development committee;
- To oversee the preparation of data reports for review by the Data and Safety Monitoring Committee at least twice each year;
- To oversee the preparation of performance monitoring reports in support of the Clinic Monitoring and Treatment Monitoring Committees;
- To advise the Principal Investigator and Director on hardware, software, and personnel requirements;
- To do any necessary programming for data analysis under the supervision of the Principal Investigator and Biostatisticians;
- To supervise the data assistant in data management activities;
- To assure that adequate documentation of the data reporting system is available at all times;
- To prepare and maintain documentation of programs, procedures, and file structures;
- To assure that adequate procedures have been established and maintained for preserving the integrity and security of the data files extracted from the CRCU database;

- To advise the investigators on all activities that interface with the data reporting system;
- To develop a reporting system of outstanding forms and materials for clinical sites;
- To develop a reporting system of outstanding gradings for the OCT Reading Center and Photograph Reading Center.

The Data Assistant is responsible for assisting the Systems Analyst with operation of the data management system.

The **Data Assistant** responsibilities are:

- To function as backup data entry staff in the event a clinic is unable to perform web-based data entry;
- To maintain an electronic registry of staff names, addresses, telephone numbers, FAX numbers, and e-mail addresses for all study personnel;
- To data enter SAE reporting forms received from clinical centers ;.
- To fax/email/mail appointment reminders and notices to Clinic Coordinators each month;
- To file study-related forms and reports in a secure location;
- To photocopy forms, the *Manual of Procedures*, and other materials when requested;
- To print mailing labels for all CATT personnel;
- To assist with the preparation and assembly of reports;
- To assist all Coordinating Center staff members as necessary to meet the needs of the Study.

The **Office Manager** provides administrative support to the Coordinating Center. Specific responsibilities include:

- To perform word processing for the highly-formatted data collection forms and revised components;
- To maintain the CATT 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 an electronic and paper history file of all versions of the *Manual of Procedures*;
- To place orders for materials and track their status;



- To develop layout and final copy for special study materials such as patient and clinical center staff newsletters;
- To develop slides and other materials for study-related presentations;
- To make travel arrangements for Coordinating Center personnel and for members of various CATT committees;
- To oversee preparation and assembly of Study documents and reports;
- To perform final formatting and distribute minutes of the meetings of the Data and Safety Monitoring Committee, Clinic Monitoring Committee, Treatment Monitoring, and Investigative Group;
- 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 Director with budget preparation for annual continuation applications;
- To type CATT correspondence as necessary;
- To format and type agendas, site visit reports, manuscripts, slide images, and other materials required for study meetings;
- To assist the Coordinating Center Principal Investigator and Director as necessary to meet the needs of the study.
- To make arrangements for study meetings, including contacting hotels, reserving rooms and equipment, identifying participants, and authorizing payment of bills.

The **Senior and Junior Biostatisticians** work closely with the Principal Investigator in activities related to data analysis and interpretation. The Junior Biostatistician is largely responsible for carrying out analyses designed by the Senior Biostatistician and Principal Investigator.

Specific responsibilities of the Senior Biostatistician include:

- To consult with the Principal Investigator and 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 develop analyses of the data required for adequate monitoring of all aspects of treatment benefit or harm, in consultation with the Principal Investigator;
- To perform analyses aimed at detection of outliers and data patterns that may indicate irregularities in data collection procedures;
- To develop, document, test and maintain statistical analysis programs for study outcome data;

- To assist the Systems Analyst in incorporating appropriate statistical summary measures and tests in routine reports;
- 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 the study writing committees by preparing accurate and timely analyses of the data, as requested;
- To develop new statistical methodology as indicated and to present and publish such methodology appropriately;
- To perform other data analytic tasks as directed by Principal Investigator and Study Chairman.

Clear communication between the Coordinating Center and the CRCU are essential to providing an efficient and responsive data management system. Specific responsibilities of the **CRCU Technical Director** are:

- To collaborate with the Coordinating Center Systems Analyst on the overall design of the CATT data management system, taking the lead role on the development and deployment of the web-based data capture system while the Systems Analyst leads in the specification and project management aspects;
- To supervise the CRCU project team of systems analysts and programmers who support the web-based data capture system;
- To ensure that the detailed logical and content checking for each data collection form, as specified by the Systems Analyst, are implemented in a timely and accurate way;
- To oversee the changes to the data capture system required to accommodate changes in the data collection forms;
- To ensure that personnel who staff the CRCU Help Desk are fully knowledgeable about the study and any trial-specific customizations to the data capture system;
- To develop a User's Manual for the clinical centers;
- To provide training sessions on the data entry system for the clinic coordinators during the initial Investigator's Group Meetings;
- To provide updates and clarifications on use of the data entry system during the course of the trial to the Director for distribution to the clinical center staff.

### **16.3. Randomized Treatment Allocations**

The Coordinating Center will generate schedules of randomly assigned treatment allocations that will be computer generated and stratified by clinical center. A permuted block method of randomization will be used to ensure balance over time and a randomly selected block size will be used to further thwart any possible attempts to determine the next treatment allocation based on perceived knowledge of previous allocations.

#### **16.3.1. Patient Enrollment and Assignment to Treatment Group**

##### **16.3.1.1. Description of the Data Capture System**

The CATT data capture system is a collaborative effort between the Center for Preventive Ophthalmology and Biostatistics and the Clinical Research Computing Unit, both at the University of Pennsylvania. The CRCU has a large staff with expertise in hardware technology and data management systems dedicated to providing state-of-the-art support services. Database security, to protect from both internal (user) breaches and external breaches, has been an area of particular development. The CRCU currently supports several ongoing clinical trials and clinical trial networks, including trials regulated by the FDA. CRCU procedures conform to FDA Bioresearch Monitoring Program and International Conference on Harmonization (ICH) guidelines.

Database management systems are developed as sets of applications using Oracle Clinical™, which resides on the Oracle Relational Database Management System. The CRCU staff develops project specific standard operating procedures. All programming is performed according to written Standard Operating Procedures and specifications that describe the features and functions of the system. Prior to deployment and use by Clinical Center and Coordinating Center personnel, the electronic systems are subjected to extensive testing. This testing is conducted according to a written test plan and is intended to validate the proper functioning of the system. Once the system has been tested and validated, it is migrated from a 'development' environment and is deployed in a 'production' environment. Modifications to the system are requested using standard operating procedures, resulting in development of written specifications that explicitly document programming requirements. Following modification to the system, the system is re-subjected to testing and validation before being deployed in production mode.

To achieve World Wide Web distribution of the system, a three-tiered Web Computing Architecture is utilized that consists of the (i) SUN Enterprise 4000 Oracle RDBMS Server that will provide secure access to the databases, (ii) the DELL Web Application Server, and (iii) the Client PC.

Part of the training meeting for the study was devoted to training users on accessing the data system for the trial. Users' manuals on data entry procedures and trouble shooting are prepared by CRCU and distributed by Coordinating Center staff. A CRCU Help Desk provides telephone and email support services for connectivity and access issues for the clinical center staff.

### **16.3.1.2. Enrolling the Patient into the CATT Study**

All patient data, including eligibility determination, randomization, and follow-up, is completed via the Web-based distributed data management system. After a patient has been evaluated for the study at the clinical center and the study ophthalmologist determines that the patient is eligible, the pre-randomization data collection forms (baseline forms) for the patient is entered into the database by the Clinic Coordinator. Critical fields are double keyed; each screen is reviewed by the Clinic Coordinator before saving. Validation of data occurs during and after the data entry session. Electronic logs of the completion status of each form and assessment are tracked by the Coordinating Center to determine the status of data collection for each registered patient. (Refer to the User's Manual for additional information about the data management system.)

To receive a randomized assignment for a patient, an on-line Randomization Module will be available for use by clinic coordinators. Prior to actual patient randomization, the system performs a check of the eligibility data to confirm eligibility. Once eligibility is confirmed, the system informs the clinic coordinator to which treatment group the patient has been assigned. The clinic coordinator is then instructed to print this screen and to file it with the Patient Registration Log. To preserve masking of other study staff, do **NOT** file this screen in the patient's study file! An appointment schedule customized to the patient is also made available at the time of randomization. The clinic coordinator should thrice print this appointment schedule and file one copy in the patient's study file and the other copy with the Patient Log and/or follow-up schedule notebook. The third copy should be given to the patient. A secured hard copy of the order of treatment assignment is also available to the senior Coordinating Center staff in case of computer or Web connectivity problems. In these cases, the steps used for confirmation of eligibility will be replicated by reviewing faxed copies of completed baseline data collection forms.

## **16.4. Data Control and Data Management**

### **16.4.1. Initiation of Patient Records**

The CATT data management system (see Exhibit 18-2) begins for each patient with the registration of a patient for the trial and subsequent randomization of a patient to a treatment group. Thereafter, all data from the clinical centers are checked against the registration files with regard to ID number and ID alphabetic code before acceptance into the CATT system.

### **16.4.2. Design of Data Collection Forms**

Design of data collection forms and administrative forms is the responsibility of the Data Forms Development Committee, led by the Director, with the Systems Analyst, Protocol Monitors, and representatives of the Photograph Reading Center and OCT Reading Center as members. Draft forms are circulated to the Principal Investigators of the Coordinating Center, OCT Reading Center and Photograph Reading Center, the CRCU, and the Study Chairman for review and comment. Near the time of finalization, the draft forms are also provided to a few clinic coordinators for review and comment.

The CATT data collection forms are designed to facilitate accurate completion and 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 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.

### **16.4.3. Data Entry**

All data entry is performed by the Clinic Coordinators or certified clinic staff under the supervision of the Clinic Coordinators. Each item entered is checked for valid codes, legitimate ranges, legal dates, etc. Invalid entries are flagged. Sections of the forms that are complete may be data entered and sections that are incomplete may be data entered later. Form revisions and additions are accommodated by having data management staff modify or create the appropriate data definition.

The CATT database is extracted from CRCU servers to the CPOB server on a daily basis. The additional tasks of performance and treatment monitoring, further quality assurance measures, and analysis are the responsibility of the Coordinating Center staff.

### **16.4.4. Data Edits**

Data that have been entered into the Web-based system are subject to additional consistency checking involving more complex logic than implemented during data entry checking. Often these post-entry checks involve several different forms and visits. The Systems Analyst develops the logic for these study-specific checks and the comments to be associated with the resulting data queries. These instructions are incorporated into the CRCU data system by CRCU staff.

The Clinic Coordinator reviews online edit messages and the corresponding data forms. If necessary, the Clinic Coordinator corrects the paper form, initials and dates the form, and updates the online database.

The updated data records are again subjected to the entire data checking system. 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 Director, flag specific items on specific forms as exempt from further edit.

The CRCU system generates electronic transaction records after every record correction so that a full verifiable audit trail is created.

#### **16.4.5. Backup of the CATT Database**

The CATT database, data management system, and data analysis system represent the efforts of the entire Investigative Group over the duration of the study. All study data entered through the Web-based system is backed up on the CRCU servers and their offsite storage. The database is extracted daily to the Coordinating Center servers. Data files reside on the CPOB file server and are backed up nightly. A rotation of backup tapes is maintained so that the database can be restored as of the most recent day of the week, week, month, or quarter. A copy of the monthly backup tapes is also stored off site. In addition, all CATT CPOB personnel are required to keep copies of key documents such as forms, correspondence, and reports 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.

#### **16.5. Quality Assurance Activities Related to Data Management**

The overall quality assurance program for the study is described in Chapter 13. Specific quality assurance features related to data management are:

- Standard data collection forms and procedures;
- Training and certification in data collection and data entry;
- Central concurrent processing of data to detect problems early and provide feedback to the clinical centers;
- Data edits for missing, invalid, and suspect responses;
- Regular reporting on performance of all centers;
- Double entry of critical data fields
- 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 at the particular clinical center;
- Checking a random 10% sample of original data collection forms against medical records during site visits.
- Explicit instructions with each distribution of new data collection form masters about new/revised questions and instructions to discard all previous versions and copies.

##### **16.5.1. 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 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) is determined based on the keystrokes and fields checked. The nature of any discrepancy is investigated to identify any systematic problems.

The process by which this activity will occur is listed below:

- During initial data entry, the CATT clinic coordinator is required to double enter the data within critical fields.
- The system queries all data discrepancies.
- The Systems Analyst draws a 5% random sample of forms that were entered into the database for which all edit queries were resolved within a specific period of time, usually one month, and ask the clinic coordinators to send copies of the paper forms to the Coordinating Center. All form types that were entered during that period are subject to selection. The Data Assistant at the Coordinating Center and the Protocol Monitor will compare the content of the submitted form with the CATT database on an item-by-item basis. Non-matching data will be resolved by data entry queries initiated by the Coordinating Center.
- Upon completion of the data checking, the copied data collection forms are filed at the Coordinating Center. The Systems Analyst tabulates the total number of fields and keystrokes that were included in the sample and the number of discrepancies noted 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.
- 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.
- These counts, the time period the forms were data entered, and the person who entered the data will be available for future tabulations for review by the Data and Safety Monitoring Committee.
- The Systems Analyst provides the Director with the discrepancy counts as described above for each period, as they are performed.

#### **16.6. Special Reports Developed by the Coordinating Center**

The Coordinating Center provides reports based on available information to support the clinical centers, the quality assurance activities of the study (see Chapter 11), and the periodic meetings of the Operations Committee, Executive Committee, Clinic Monitoring Committee, Treatment Review Committee, Investigative Group, and Data and Safety Monitoring Committee.

### **16.6.1. Creation of Data Sets for Reporting**

Certain reports that are designed to check the completeness of activities in the clinical centers, Reading Centers and Coordinating Center are run on the current database, usually involving the master files and auxiliary files and programs that identify and count specific data collection forms 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. Therefore 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. Clinic Coordinators will be encouraged to resolve any known data entry backlogs. 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.

### **16.6.2. Creation of Data Extracts**

The frozen datasets consist of the full complement of SAS system files that are updated daily from the CRCU Oracle databases 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, changes in visual acuity, changes in subretinal or intraretinal fluid on OCT and adverse events.

### **16.6.3. Database of Tables**

During the course of the study, hundreds of tables will be used for the various committee meetings. Some tables are used in reports to several committees. 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, etc.). A paper file contains the latest hard copy version of the table, as well as the output supporting the table. The Director maintains a master list of working tables. For a particular report, the working tables may be put into any order.

## **16.7. 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 CATT investigators, with funding renewals or initiatives, or with continuing data monitoring.



## **16.8. Administration of Subcontracts with Clinical Centers and Administering the Payment Plan for Patient Care Costs**

The Principal Investigator of the Coordinating Center holds responsibility for administration of the Purchased Services Agreements with the clinical centers. Staff members from the research support services units of the Department of Ophthalmology and the University of Pennsylvania provide the subcontracting documents after receiving specifications of the terms from the Principal Investigator. These staff members produce the documents, distribute the documents to the clinical centers, respond to queries regarding the terms of the contract, negotiate changes in language, periodically request invoices from clinical centers, execute procedures to provide payment, and resolve accounting discrepancies. In addition, these staff members solicit and follow-up on the materials needed each year to fulfill requirements for non-competing renewals of grant awards and the execution of new subcontracts each year. The Principal Investigator reviews paperwork for all payments to clinical centers and intervenes when administrative processes appear to be stalled at either the University of Pennsylvania or one of the clinical centers.

Costs associated with patient care are reimbursed on a per visit basis; patient care payments will be made only after all the required material (case report form, OCT scan, photographs) are submitted from the clinical center.

## **16.9. Preparations for Study Meetings**

A major factor in ensuring protocol adherence and good communications among study personnel in the various functional units is the Investigative Group meeting held once each year. The Coordinating Center staff members play a major role in preparing for these meetings. Similarly, Coordinating Center personnel provide materials and support for meetings of the Operations Committee, Clinic Monitoring Committee, Treatment Review Committee, Data and Safety Monitoring Committee and SAE reviews by the Medical Safety Monitor.

The Principal Investigator of the Coordinating Center prepares the meeting agendas in consultation with the Study Chairman and other members of the Operations Committee. The agendas guide the assembly and preparation of materials to be discussed at the various meetings. Meeting notebooks are prepared by the Coordinating Center to facilitate the discussions of the Executive Committee and Investigative Group.

All logistical support for Study in-person meetings and teleconferences is provided by Coordinating Center staff. The Office Manager bears responsibility for most of these functions.

Copies of minutes are filed in the CATT Library maintained at the Coordinating Center.

## 16.10. 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 Office Manager. The following documents are kept in the CATT Study Library for reference by Coordinating Center staff and other study investigators:

- Minutes of meetings:
  - Operations Committee
  - Executive Committee
  - Investigative Group
  - Clinic Monitoring Committee
  - Treatment Review Committee
- Investigative Group Progress Reports
- Site visit reports
- Reports from triannual 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
- Protocol memoranda
- Archive of previously used versions of data collection forms
- Log of Extraordinary Events
- Reprints of study publications.

Other materials may be added to the Library as directed by the Coordinating Center Principal Investigator. Copies of confidential data reports and meetings of the DSMC are kept in locked filing cabinets in individual staff offices.

## 16.11. Coordinating Center Handbook of Procedures

The Coordinating Center Office Manager and other personnel designated by the Principal Investigator 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 provide step by step instructions for data management tasks as well as many of the other activities of the Coordinating Center.

## **16.12. Meetings of the Coordinating Center**

Meetings of all members of the Coordinating Center will occur monthly, or more frequently as required. Such meetings allow all members to remain up-to-date on study progress and discuss all aspects of a problem and ways to resolve it.

## **16.13. Training and Certification of CATT Personnel**

One important function of the Coordinating Center is the development and administration of the CATT Training and Certification Program. Careful adherence to all protocols in every aspect of the study, including treatment procedures, visual acuity testing, and the data collection and data entry process is essential to the success of the trial. The quality of study data depends upon uniformity of procedures and data collection and careful data entry. Therefore, standardized training on all protocols and data collection procedures, along with certification of CATT personnel, are important components of quality assurance.

The CATT Operations Committee oversees the design and implementation of the training program and sets the certification requirements for all CATT personnel. The Coordinating Center is responsible for reviewing completed certification requirements, developing the on-line system for completing knowledge assessments, providing customized feedback, issuing certification numbers, and maintaining the electronic and paper roster of all certified study personnel.

Training of clinical center staff who will be certified as Clinic Coordinators, Ophthalmologists and OCT Technicians for the study occurred at the CATT Training Meetings and consisted of the following four modules:

- Proficiency in all examination procedures
- Knowledge of the treatment protocol
- Data collection and quality assurance
- Submission of OCT images

The training sessions consisted of both presentations and “hands-on” training that provided ample opportunity for discussion on every aspect of the study and the Manual of Procedures (MOP).

The data collection component of the training included instruction in accessing the database, submitting “test” data into the on-line system, and simulated data containing errors and omissions to demonstrate common problems and evaluate the ability of study personnel to collect data accurately.

### **16.13.1. Certification**

CATT Study personnel must be certified before performing any study procedures. All people seeking certification will receive a checklist of certification requirements that

must be met for each study-specific role prior to any interaction with study patients. Checklists and materials needed to complete certification requirements are available on the CPOB website at [www.cpob.org/studies/catt/certification](http://www.cpob.org/studies/catt/certification).

The certification of clinical center staff is primarily web-based. All individuals seeking certification in any study role must first register on the CATT certification website. The Protocol Monitor, after checking the name from a roster of potential study clinical center staff, activates the account. Upon activation, the individual seeking certification can read the requirements for certification and begin the certification process. (See Chapter 14 for more details regarding the certification system and certification requirements.) After satisfactory completion of all certification requirements, the certification website notifies the newly certified staff member and the Clinic Coordinator at the site. When a Clinical Center achieves certification, a letter is sent to PIs and Clinical Coordinators listing all certified personnel (and their certification numbers) at their clinical center.

The names of all certified personnel are entered on the roster of certified personnel. The Director of the Coordinating Center provides certification update reports to the CATT Study Operations Committee.

#### **16.13.1.1. Updating Certification**

Maintaining certification in some CATT roles (i.e., Refractionists and Visual Acuity Examiners) is contingent on performing the procedure within a specified time period (see Chapter 14). If study personnel have not performed the procedure for which certification was issued within the specified time, the person will be de-certified for the role and the Principal Investigator and Clinic Coordinator for the site will be notified. Termination of employment at the Clinical Center automatically cancels certification for an individual unless they are transferring to another study Clinical Center.

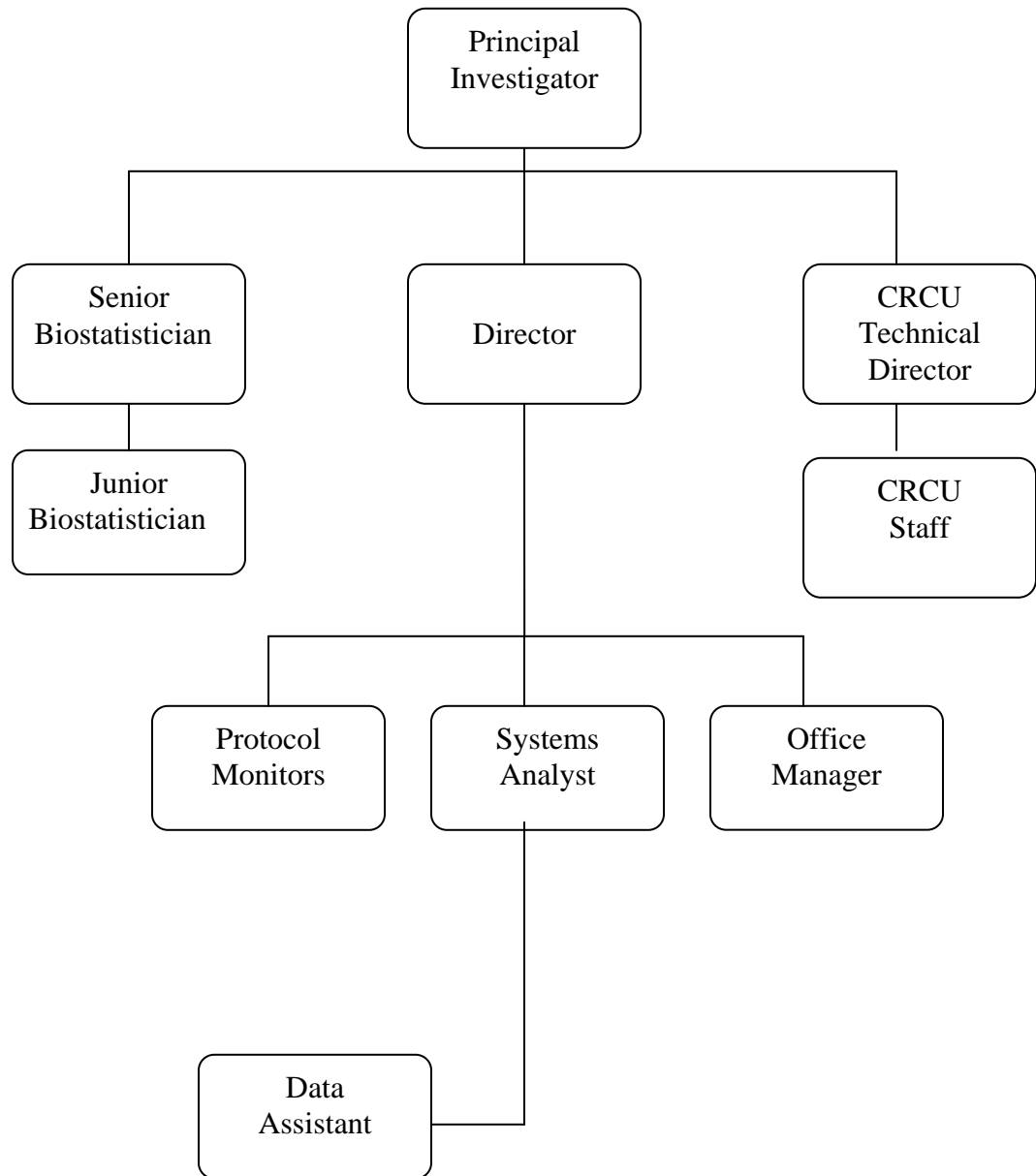
#### **16.14. CATT Website**

The Coordinating Center maintains a website to provide information about the trial to the public and prospective patients, as well as to study staff. The website is a component of the CPOB website (<http://www.med.upenn.edu/cpob/>).

Visitors to the website will have access to a description of the study that includes information on age-related macular degeneration, a listing of CATT clinical centers and resource centers with complete contact information, the Manual of Procedures, links to websites on age-related macular degeneration and addressing participation in clinical trials, copies of previously distributed CATT patient newsletters, and CATT publications.

**EXHIBIT 16-1**

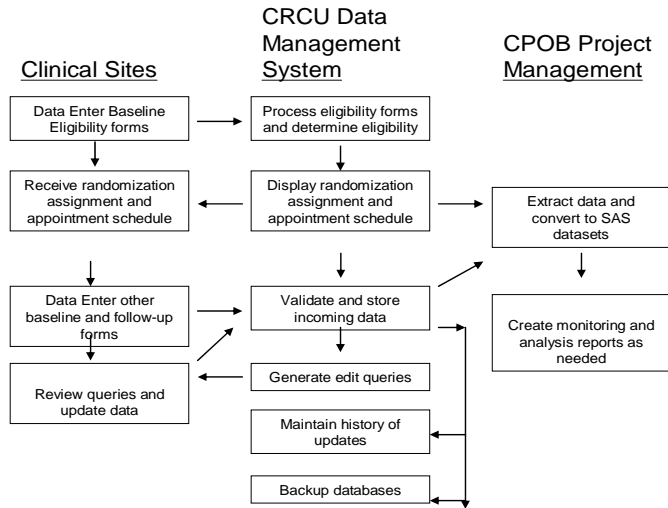
**CATT COORDINATING CENTER ORGANIZATIONAL CHART**



## EXHIBIT 16-2

### CATT STUDY DATA SYSTEMS

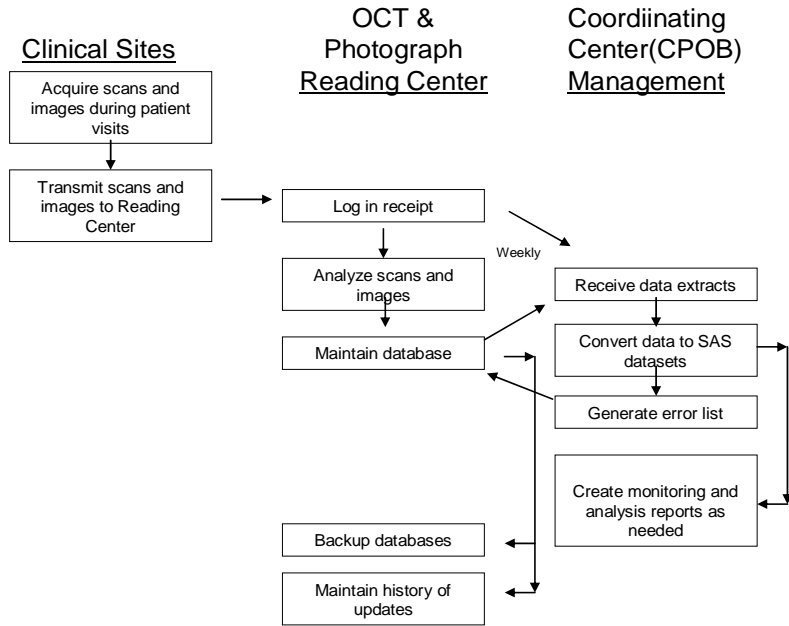
#### Data from Clinical Centers



# EXHIBIT 16-3

## CATT STUDY DATA SYSTEMS

### Data from the OCT & Photograph Reading Centers



## CHAPTER 17

### FUNDUS PHOTOGRAPH READING CENTER OPERATIONS AND PROCEDURES

#### 17.1. RESPONSIBILITIES OF THE FUNDUS PHOTOGRAPH READING CENTER

The CATT Fundus Photograph Reading Center's (CATT FPRC) responsibilities are to ensure good quality photographs and angiograms by implementing certification of photographers and digital imaging systems, providing detailed photography procedures for the clinical centers; identifying and executing a grading protocol; and monitoring photographic performance at the clinical centers. To facilitate discussion, the responsibilities of the CATT FPRC are organized according to the phases of the study.

- Initial design and protocol development
- Final preparation for trial initiation
- Patient recruitment, treatment, and follow-up
- Patient closeout
- Termination of the trial

##### 17.1.1. Initial Design and Protocol Development

During the initial design phase of CATT, the FPRC staff engaged in the following activities:

- Establishing and validating an image data base structure for the receipt and management of digital images
- Initial testing and refining of the image database structure
- Drafting forms for submission of photographic materials
- Establishing an inventory system for non-digital photographic materials received
- Collaborating with the CATT Planning Group in the selection of clinical centers to participate in the trial
- Establishing the grading protocol incorporating photographic eligibility and classification of CNV at follow-up visits
- Drafting chapters for the *Manual of Procedures*
- Developing and validating procedures to certify digital imaging systems at clinical centers
- Developing quality assurance procedures for the FPRC aspects of the trial

##### 17.1.2. Final Preparation for Trial Initiation

Prior to initiating CATT, the staff at the FPRC will perform a number of activities in order to begin the trial with qualified and certified clinical centers as well as an established FPRC. These activities include:



- Implementing certification of digital imaging systems at clinical centers
- Implementing certification of photographers and ophthalmologists at clinical centers
- Collaborating with the Coordinating Center to finalize the quality control program for image grading
- Refining and finalizing the grading protocol incorporating photographic eligibility and classification of CNV at follow-up visits
- Testing and refining the photographic data processing procedures
- Developing a website page for photography/imaging needs of CATT as part of the study website
- Fine tuning the data collection activities at the CATT FPRC in conjunction with the activities of the CATT Coordinating Center
- Participating in the execution of initial training sessions for clinic personnel to review study design, data collection methods, and procedures for interfacing with the CATT Resource Centers
- Collaborating with the CATT Coordinating Center to refine the editing and logic checking of photograph gradings
- Collaborating with the CATT Coordinating Center to develop power point presentations for local clinic site use to address local physician groups for enrollment
- Establishing formats for clinic performance monitoring reports
- Participating in a meeting of the Data and Safety Monitoring Committee to review the protocol

### **17.1.3. Patient Recruitment and Follow-up**

Activities during this phase can generally be categorized as administrative, data collection and processing, photograph reading, data analysis and reporting, quality assurance, and planning for future phases. CATT FPRC 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 CATT meetings
- Assisting the staff at each clinical center to interpret and follow the protocol and procedures relating to the CATT FPRC as documented in the *Manual of Procedures*
- Maintaining certifications of photographers and digital imaging systems

#### *Material Collection and Processing*

- Maintaining an inventory, tracking, and storage system of all materials received at the CATT FPRC

- Confirming that all photographic materials received from the clinical centers are identified and labeled consistently and accurately
- Conveying the photographic data collected at the CATT FPRC 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 CATT Grading Protocol in order to:
  - ▶ Document that patients selected for the Study at the various clinical centers meet the angiographic and photographic eligibility criteria specified (Baseline Eligibility and Lesion Description)
  - ▶ Identify secondary outcome measures at follow-up, when applicable
  - ▶ Interpret the follow-up photographs for CNV lesion status (Lesion Description at Follow-up)

#### *Data Analysis and Reporting*

- Preparing reports for the Investigative Group concerning the adherence to the eligibility criteria, status of receipt of initial visit and follow-up photographs, 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 CATT
- Participating in the drafting of all CATT publications
- Performing other activities deemed appropriate by the Steering Committee and Data and Safety Monitoring Committee, or other Study investigators as time permits
- Reporting to appropriate audiences FPRC methodological innovations developed during the course of CATT

#### *Quality Assurance*

- Participating in the initial training sessions for clinic personnel to review study design, data collection methods, adverse event reporting, and procedures for interfacing with the CATT OCT Reading Center, the CATT FPRC, and the CATT Coordinating Center
- Masking of all photographs as to the randomization assignment
- Performing Quality Assurance procedures of the established CATT grading protocol

- 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 CATT FPRC
- Maintaining documentation of all procedures and operations at the FPRC
- Maintaining the photographic files in a secure manner to assure their integrity
- Backing up the CATT FPRC data files to assure that data are not lost
- Reporting periodically on the quality of the data accumulated at the CATT FPRC to the Executive and Data and Safety Monitoring Committees
- Cooperating with any individual or group assigned to review operations at the CATT FPRC

*Planning for Future Phases*

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

**17.1.4. Patient Closeout**

As with earlier phases of CATT, during the Patient Closeout phase the primary responsibilities of the FPRC staff are concerned with coordinating, developing and refining closeout procedures, and data processing and analysis. Specific responsibilities during this period are:

- Confirming that all gradings are complete and finalizing database of grading records
- Responding to any final photographic data queries from the Coordinating Center as required for final data analysis
- 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 digital image files and photographic materials
- Participating in manuscript writing activities

### 17.1.5. Termination of the Trial

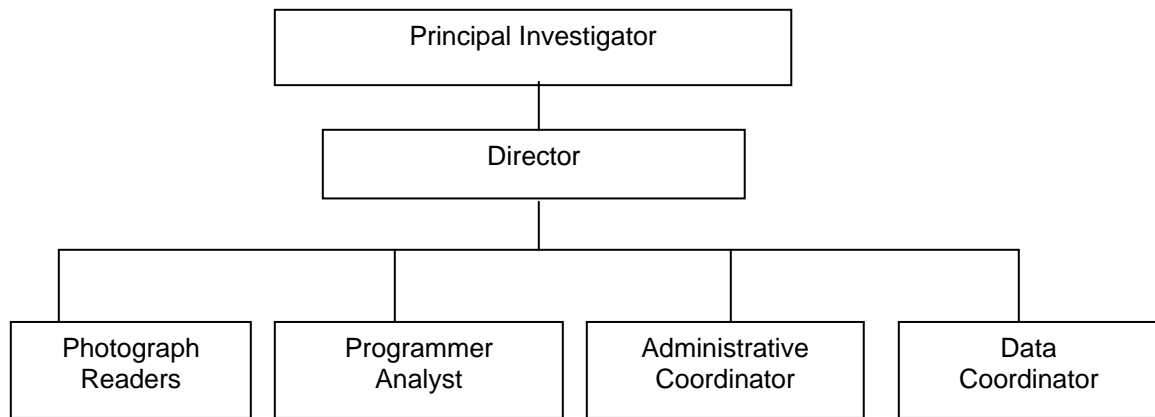
During the last phase of CATT for which funding is available, the FPRC may be only minimally funded. The following activities are those anticipated for the FPRC during this period:

- Participating in the completion of manuscripts for publication which may require access to the photographs for illustrations
- Placing of digital images, photographic files, and other materials in the selected archives

## 17.2. ORGANIZATION OF THE FPRC

### 17.2.1. Internal Organization

The staff of the FPRC includes the following individuals: Principal Investigator (ophthalmologist); Director; Fundus Photograph Readers; Programmer Analyst; Administrative Coordinator; and Data Coordinator. The responsibilities and level of effort for these staff members is based on the workload anticipated for CATT.



### 17.2.2. Personnel Responsibilities

**Principal Investigator:** The Principal Investigator is responsible for the overall performance of the CATT FPRC. Specific responsibilities in this role include:

- Reviewing all baseline photographs to ensure compliance with the photographic and angiographic eligibility criteria
- Collaborating with the Director to maintain and refine the grading program
- Serving as the clinical director of the FPRC
- Assisting with FPRC procedural changes involving the interpretation of photographs
- Organizing research efforts for publications involving FPRC data and methods

- Collaborating with the CATT OCT Reading Center to facilitate comparisons of OCT scan and angiographic data
- Serving as a voting member of the CATT Operations Committee
- Serving as a voting member of the CATT Executive Committee

**Director:** The Director is responsible for the day-to-day operations of the FPRC. Specific responsibilities include:

- Organizing and supervising daily operations
- Recruiting and training of FPRC personnel
- Designing and executing the reader training program to ensure that adequately trained grading staff is available throughout the term of the study
- Reviewing all baseline photographs to ensure compliance with the photographic and angiographic eligibility criteria
- Collaborating with the CATT OCT Reading Center to facilitate comparisons of OCT scan and angiographic data
- Supervising the readers
- Collaborating with the FPRC Principal Investigator regarding clinical interpretation of photographs
- Designing appropriate data collection forms
- Serving as a photograph reader as needed
- Communicating with clinical centers on issues of patient eligibility and clinic performance
- Participating in administration of certification procedures for ophthalmologists
- Supervising certification procedures for study photographers
- Assisting in training ophthalmologists and clinic coordinators at Study Group Training Meetings
- Serving as a voting member of the CATT Operations Committee
- Serving as a voting member of the CATT Executive Committee
- Establishing and overseeing the FPRC Quality Assurance (QA) procedures
- Serving on the CATT Clinic Monitoring Committee
- Serving on the Data Forms Development Committee
- Coordinating the Data Checking Program of FPRC database
- Serving as liaison with Coordinating Center regarding FPRC database issues, photograph interpretation, data queries, and other data collection issues
- Coordinating resolution of photographic data queries from the Coordinating Center

- Updating FPRC related chapters in the CATT Manual of Procedures
- Developing a FPRC Handbook of Procedures
- Administering FPRC budget and reviewing monthly budget reports
- Preparing grant continuations and renewals for review and approval by the FPRC Principal Investigator
- Preparing presentations for Study meetings and scientific forums
- Assisting in preparation of general study publications
- Participating in research efforts for publication of FPRC methods

**Fundus Photograph Readers:** The Fundus Photograph Readers are responsible for the evaluation and interpretation of study photographs, angiograms, and digital images. The specific responsibilities of the readers may include any or all of the following:

- Identifying inclusion and exclusion criteria on initial visit photographs and angiograms of patients enrolled in the study
- Evaluating initial visit photographs for detailed description of the CNV lesion
- Evaluating follow-up visit photographs compared to initial visit photographs for lesion changes
- Evaluating quality of photographs graded
- Resolving photograph grading data queries as identified by the Coordinating Center
- Participating in QA Grading procedures
- Participating in data checking procedures of the FPRC database
- Participating in Study training meetings
- Participating in Study Group meetings, and attending Ophthalmologist workshops at those meetings
- Assisting with administrative tasks as needed

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

- Confirming receipt of all photographic materials received at the FPRC
- Checking all materials for completeness and consistency of labeling
- Interacting with clinical centers regarding photographic materials issues
- Notifying clinical centers and resolving any discrepancies of identifying information
- Establishing FPRC patient files as patients are enrolled
- Transferring digital images from CDs to the FPRC image database server

- Running the adjudication program daily to identify photographs that have been graded by both readers
- Preparing materials for the grading process
- Performing data entry of all inventory forms
- Responding to data queries as appropriate
- Filing and retrieving all study film-based photographs from study files
- Preparing materials for data checking and materials checking programs
- Preparing photographs for QA cycles
- Assisting with word processing and graphics as needed
- Assisting all FPRC staff members as necessary to meet the needs of the Study
- Attending Study Group meetings

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

- Supervising the FPRC data coordinator
- Prioritizing workload of the FPRC data coordinator
- Coordinating the implementation of the QA Grading system
- Maintaining records of all FPRC form revisions
- Participating in the study training meetings
- Assisting with training of clinic coordinators
- Serving as liaison with Coordinating Center as appropriate
- Participating in development of FPRC Handbook of Procedures
- Participating in Study Group meetings
- Maintaining budget and monthly reporting of expenditures
- Assisting with preparation of annual budget for grant continuation

**Programmer Analyst:** The Programmer Analyst is responsible for the development and implementation of the digital imaging data base, computer assisted grading programs, and development of innovative computer applications for grading digital images. Specific responsibilities include:

- Maintaining and securing the FPRC image data base
- Collaborating with the FPRC PI and Director to ensure that submitted digital images can be accessed at the FPRC (implementation of a Submission Module)
- Establishing a data entry system for the inventory of all materials received at the FPRC (implementation of a CATT Receipt Application)

- Collaborating with the FPRC PI and Director on the development and implementation of the grading protocol for digital images
- Collaborating with the FPRC PI and Director to maintain and refine the grading program
- Collaborating with the CATT OCT Reading Center to facilitate comparisons of OCT scan and angiographic data
- Planning, budgeting and implementing acquisition of new computer hardware and expanding digital storage capabilities
- Researching and implementing new robust technologies to improve accuracy and speed of grading digital images
- Collaborating with the Coordinating Center for compatibility of data records and security issues
- Performing edits and data queries on photograph inventory data base
- Maintaining customized image archiving software
- Applying custom image format RIF to FPRC modules
- Facilitating troubleshooting at the Clinical Centers regarding digital imaging issues
- Implementing and maintaining the FPRC page for the study website
- Training digital image support personnel
- Training readers in using the hardware, software tools and network connectivity
- Assisting in training ophthalmologists and clinic coordinators at Study Group Training Meetings
- Administering certification procedures for imaging systems and fundus cameras
- Participating in Study training meetings

The Programmer Analyst is responsible also for maintenance of hardware and software tools to allow the FPRC to efficiently and securely support study goals. Specific tasks to accomplish this are:

- Maintaining the FPRC server and administering the FPRC network
- Performing regularly scheduled back up of the server including storage of the back up copy off site
- Maintaining the database for storage and access of the digital images for grading
- Upgrading and expanding the software and hardware capabilities
- Establishing the user specific and password protected data entry systems for use within the FPRC
- Working with other staff members in troubleshooting grading software



### **17.3. CERTIFICATION OF CATT FPRC STAFF**

All personnel in the Coordinating Center, FPRC, OCT Reading Center, and Chairman's Office must fulfill specific criteria. Individuals seeking certification must demonstrate proficiency in the tasks they are expected to perform for CATT, in addition to completing both a general knowledge assessment about the study and a role specific knowledge assessment. The FPRC staff is required to read the entire CATT MOP.

#### **17.3.1. Readers**

Although photograph Readers may be certified for other studies, they are required to complete the CATT General Knowledge Assessment and the CATT Photographer Knowledge Assessment questionnaires and demonstrate a thorough understanding of the CATT grading system by grading a sample of photographs using the CATT grading protocol.

For newly hired readers, the reader-training program consists of two phases. The first phase of the training program (initial reader training) includes knowledge and understanding the anatomy and pathology of the eye; identification of features of AMD, including determination of drusen size and area, identification of neovascularization, serous detachment of the pigment epithelium and geographic atrophy on stereo color fundus photography and fluorescein angiography. Once these features are understood, the grading protocol is introduced. For a reader trainee this process may take 3 to 6 months. Practice grading forms are completed. Gradings are performed openly and clarifying questions are encouraged. The gradings are reviewed with the FPRC PI and Director for clarifications and questions. When the readers are skilled in identifying the pathology, and when such skills are demonstrated to the satisfaction of the Principal Investigator and Director, then the readers are ready for Phase 2.

For experienced readers the certification process starts with Phase 2.

The second phase of reader training involves independent grading of photographs of patients who would qualify for CATT to gain more experience and practice with the CATT grading protocol. The Principal Investigator and the Director review the completed gradings. Once these gradings demonstrate the reader's ability to apply the grading protocol, the reader grades the certification sample to become certified. A newly certified reader will serve as a first reader with the second reader being an experienced reader (such as the Principal Investigator and the Director). When the second (more experienced) reader determines that the level of adjudication is acceptable, the Principal Investigator is informed, and the reader may advance to an experienced reader status.

#### **17.3.2. Certification of Other FPRC Staff:**

Other FPRC staff members (including the Principal Investigator and Director) are required to complete the CATT General Knowledge Assessment and the CATT Photographer Knowledge Assessment. (See Chapters 8 and 14.)

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

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

### **17.4.1. Receipt of Photographic Materials at the FPRC**

For digital images of color photography and fluorescein angiography, the Data Coordinator at the FPRC opens the patient's file from the CD-R submitted using the CATT Receipt Application and confirms the CATT identification information on the images with the Photograph Inventory Form. The images received are displayed by the software for visual inspection and possible file reading errors that might occur during the recording and transportation of the CD-R media. If any confidential information is found on the image file or in a separate file on the CD-R disk, the image files are not transferred to the FPRC server and the CD-R is returned to the CATT Clinical Center for proper labeling of the image files. The corrected materials are then resubmitted. After the verification process is completed, the accepted images are appended to the CATT image database on the dedicated CATT image database server.

For film based images, the Data Coordinator checks that all labels have the corresponding information and that all materials indicated on the Photograph Inventory Form are present. The CATT FPRC Data Coordinator addresses any discrepancies by contacting the person who submitted the materials for resolution. All discrepancies are resolved before any photographs/angiograms are made available to the readers.

### **17.4.2. Transfer of Images to the FPRC Server**

It is the responsibility of the FPRC Data Coordinator to copy the images from the CD-R disk to the FPRC server. Images are stored, managed, and accessed from a custom developed image database, which resides on the CATT FPRC dedicated database server. The database files exist in several image copies for data protection. Backup of the data is performed daily on the removable media, which is stored in a separate location. Access to the image database will be user specific and password protected. The CD-R disks will be stored in patient files by patient identification number in a locked filing cabinet.

### **17.4.3. Inventory of Photographic Materials**

An inventory database is created by the CATT Receipt Application. This database will be used to identify received materials, materials pending resolution, those images ready for grading, and outstanding materials when compared with the Coordinating Center database of visits completed.

Inventory data that accompanies the digital files in electronic format will be included in the inventory database as well.

## **17.5. GRADING PROCEDURES**

### **17.5.1. Overview**

The CATT grading protocol is designed to confirm eligibility of patients enrolled in CATT, describe the CNV lesion at baseline and follow-up, and identify any changes in the study eye that could account for changes in vision. Any two CATT certified readers grade the photographs independently. Differences are openly adjudicated, and the adjudicated record is transferred to the database. If necessary, the Director or Principal Investigator may be asked to resolve a difficult case. Only the Director or Principal Investigator can confirm the final eligibility of a patient. The readers also assess the focus/clarity and stereoscopic quality of all photographs based on their confidence to complete the grading of the photographs.

A finding will be considered present or absent if the decision reflects 80% or greater certainty. Otherwise, lesion presence or absence will be graded as questionable. A decision of "can't grade" will be made if other fundus pathology, photographic quality, or artifact obscures the object of interest such that definitive decision cannot be made with 80% certainty.

### **17.5.2. Viewing Images**

Digital images will be viewed on an LCD color monitor using the software applications which includes methods for rendering stereoscopic images, image comparison, and measurements.

The software allows for viewing of the image files for all current ophthalmic imaging vendors. The images, acquired in stereo, can be rendered on a computer monitor in stereo (when necessary), and viewed with Screen-Vu optical stereo viewers. Distance and area measurements can be made with a mouse, and appropriate conversions are available to account for magnification differences among the various digital systems and fundus cameras.

Film based images will be viewed in stereo on a lightbox with 5x Donaldson stereo viewers as is standard practice for film based images.

Two readers will perform all photographic and angiographic image interpretation independently with disagreements openly adjudicated. The entire FPRC staff is **masked** to which treatment a study patient receives. The FPRC Principal Investigator or Director will review all initial visits. The FPRC Principal Investigator reviews any initial visits judged not to meet the eligibility criteria. Difficult cases will be brought to the FPRC Director and/or the FPRC Principal Investigator.

### **17.5.3. Preparation for Grading**

The Coordinating Center Systems Analyst confirms the study information and dates of the photographs entered into the inventory of images by the Receipt Application and generates a list of patient visit photographs cleared for grading. Discrepancies identified by the Systems Analyst are resolved before patient images are cleared for grading.

From the list of visits cleared, the FPRC Data Coordinator prepares the grading forms for each grader by providing the study ID, Alpha Code, week # and date of the photographs. The readers log onto the image server and access the appropriate patient image files for grading.

#### **17.5.4. Calibration of Monitors at Reader Workstations**

In order to achieve comparable grading results at the multiple workstations in the FPRC, the viewing parameters of the computer monitors need to be calibrated and standardized. A hardware based calibration procedure for each monitor will be used to measure the actual monitor characteristics. Based on the measurements, specially designed software will create a custom profile for each monitor. An equalization procedure is performed finally to match the multiple monitor profiles and to establish objective, highly accurate, equal display parameters for all calibrated monitors. The described procedure has been deployed, tested, and validated for existing workstations.

#### **17.5.5. Access and Viewing of Digital Images**

Digital images will be viewed on a computer monitor. Images are accessed by ID #, Alpha Code, week #, and date of photographs. Aside from viewing and measurement, the reader will not be permitted to enhance or otherwise alter the original images.

### **17.6. INTERPRETATION OF PHOTOGRAPHS**

Overview: The baseline fluorescein angiogram and color photographs are read to confirm eligibility for the study and provide a detailed description of the CNV lesion. The follow-up angiogram and color photographs are read to identify changes in the CNV lesion and other pathology that will be used to correlate with OCT obtained at the same visits.

#### **17.6.1. Baseline Eligibility and Lesion Description**

Fluorescein angiograms and color photographs of both eyes are obtained at baseline. The following features will be evaluated to determine eligibility:

- Presence of an active CNV lesion (leakage on angiogram)
- CNV or sequela of the CNV (i.e., pigment epithelium detachment, subretinal hemorrhage, blocked fluorescence, macular edema, or subretinal or intraretinal fluid) involves the center of the fovea
- Total area of fibrosis comprises <50% of the total lesion area
- >1 druse (>63 $\mu$ ) is present in either eye or late AMD in fellow eye
- No fibrosis or geographic atrophy involving the foveal center of the study eye
- No evidence of previous treatment for CNV in the study eye
- No evidence of other progressive retinal diseases likely to compromise VA within the next 3 years
- No CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia
- No tear of the retinal pigment epithelium (RPE) in the macula of the study eye
- No vitreous hemorrhage in the study eye

In addition to the features evaluated to confirm eligibility, the images acquired at baseline will also be evaluated for the following features regardless of eligibility status:

- Lesion type: [Classic CNV only, Predominately Classic CNV with some occult CNV, Minimally Classic CNV (Predominately Occult CNV with some Classic CNV) and Occult CNV only]
- Size of lesion: Measured in mm<sup>2</sup>
- Lesion location (Subfoveal/Not subfoveal)
- Component in foveal center (No lesion, CNV, SPED, SCAR, Atrophy, Hem., Fluid)
- SPED proportion of total lesion (None, < 50%, >50% of total lesion)
- Atrophic scar/fibrosis proportion of total lesion (None, < 50%, >50% of total lesion)
- CNV proportion of total lesion (None, < 50%, >50% of total lesion)
- Hemorrhage contiguous with lesion: (None, < 50%, >50% of total lesion)
- Geographic atrophy: (Yes/No)
- Subretinal fluid: (Yes/No)
- Hemorrhage present in entire macula : (None, <2, >2 disc areas)
- Retinal angiomatous proliferation (RAP) features: (intraretinal hemorrhage, fluorescein leakage, anastomosis, associated serous PED, lipid exudates)
- Tear of the RPE in the macula (Yes/No)

#### **17.6.2. Follow-up Grading**

Fluorescein angiograms and color photographs of the study eye are obtained on all patients at 012, 024, 052, 076, and 104 weeks. The images acquired at follow-up will be evaluated for the following descriptive features of the CNV lesion:

- Presence of any fluorescein leakage: (Yes/No, if Yes, border leakage or central leakage)
- Pathology in the foveal center
- Size of lesion: Measured in mm<sup>2</sup>
- Geographic atrophy (Subfoveal/not subfoveal)
- Subretinal or, intraretinal, fluid: (Yes/No)
- Serous PED (Contiguous or not contiguous with CNV lesion)
- Area of intraretinal or subretinal hemorrhage (Yes/No, if Yes, < baseline, , same, > baseline,)
- Atrophic scar/fibrotic scar (Yes/No, if Yes, < 50% or ≥ 50% of CNV lesion)

- Retinal angiomatous proliferation (RAP) features: (intraretinal hemorrhage, fluorescein leakage, anastomosis, associated serous PED, lipid exudates)
- Tear of the RPE in the macula (Yes/No)
- New “other condition” since baseline (may indicate an adverse event)

## 17.7. QUALITY ASSURANCE ACTIVITIES

The purpose of the Quality Assurance activities of the FPRC 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 readers to treatment assignment
- Re-grading subsets of photographs to ensure the reproducibility of the gradings
- Automatic edit queries and consistency checks of grading data
- Confirming accuracy of data entry
- Confirming completeness of inventory of photographic materials and their labels
- Digital imaging system certification at the clinical centers
- Calibration of monitors at FPRC staff workstations

### 17.7.1. Masking Readers to Treatment Assignment

The treatment assignment is not indicated anywhere on the Photograph Inventory Form, images, photographs, or grading forms. The FPRC Data Coordinator checks these materials to ensure that readers are masked to the treatment assignment.

### 17.7.2. Reproducibility of Gradings

The purpose of the Quality Assurance (QA) system is to monitor for temporal drift and contemporaneous variability by regrading a predetermined set of photographs and random samples of photographs by all readers at specified times. The results of the QA system identify agreement between readers as well as the reproducibility of the grading protocol.

#### **Temporal Drift**

*Initial Visits:* Replications of a structured sample of 25 patients will be performed every 3 months during enrollment. The first replication will be performed during the 3<sup>rd</sup> month of enrollment, when about 270 patients will be enrolled. The structured sample will represent a mix of eligible and ineligible patients (Baseline Eligibility Evaluation Form) with different lesion features (Baseline Study Eye Status Form) proportionate to the mix of patients from the first 3 months of enrollment. The replication gradings will include both the Eligibility Evaluation and the Baseline Study Eye Status gradings. Because study enrollment will take about 9 months, it is expected that replication grading of initial visits will take place during the 3<sup>rd</sup>, 6<sup>th</sup> and 9<sup>th</sup> month of enrollment.

*Annual Follow-Up Visits:* After 100 patients have completed their 052 weeks visit, a structured sample of 052 weeks gradings of 20 patients (5 patients in each arm) will be chosen

representing all 4 arms of the study. The sample will represent a mix of lesion features representative of the follow-up gradings (Follow-up Grading of Study Eye Form) of the 100 patients with 052 week follow-up. This replication sample will be graded quarterly until all patients have completed 052 weeks follow-up.

Similarly, after 100 patients have completed their 104 weeks visit, another structured sample of 104 weeks gradings of 20 patients (5 patients in each arm) will be chosen representing all 4 arms of the study. This replication sample will be graded quarterly until all patients have completed 104 weeks follow-up.

The CATT statistician will identify the samples for temporal drift grading. The CATT statistician will compare the replication grading results with the initial grading results to evaluate the grade-regrade agreement based on percentage of agreement, kappa and weighted kappa.

### **Contemporaneous Variability**

Replications of previous initial visit and follow-up visit gradings will be performed on a quarterly basis. The sample for each replication will be 20 patients. The first replication will be performed during the 4<sup>th</sup> month of enrollment. This replication sample will be drawn from the initial visits grading during the previous 3 months, because the only grading during this period will be for initial visits. The later replication samples will be drawn from the gradings of follow-up visits from the previous quarter. The structured samples will include patients from all 4 arms of the study and a mix of lesion features representative of the follow-up gradings (Follow-up Grading of Study Eye Form). The CATT statistician will identify the samples for each replication, and perform the data analysis to evaluate grade-regrade agreement.

### **17.7.3. Automatic Edit Queries And Consistency Checks Of Grading Data And Corrections**

The reader performs consistency checks at the time of grading. These checks include validation of patient ID numbers, alpha 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 reader reviews photographs and decides on the appropriate response. If the reader decides that a change to the grading is appropriate, the reader retrieves the original grading record through an edit mode and makes the changes. The changes are highlighted in the record to indicate a change has been made. In edit mode, the grading record is automatically stamped with the date and initials of the reader making the corrections. The reader indicates that the changes were “Coordinating Center Generated”.

When errors are identified in the grading data by a reader and a correction is made, the Coordinating Center must be informed. The reader makes the corrections to the grading record in the same manner as above, but indicates that the changes were “Reading Center Generated”.

The FPRC Data Coordinator runs a list monthly of all records with changes for review by the FPRC Director.

#### **17.7.4. Confirming Accuracy Of Data Entry**

The accuracy of the data entry system used for any FPRC Forms will be assessed on a monthly basis. A 5% random sample of all FPRC forms that were data entered is identified for a specified period of time, usually the previous month. The records identified as “the sample” are printed and each item is checked against the form in the FPRC 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 FPRC Principal Investigator, FPRC Director, and the Coordinating Center Principal Investigator, and Coordinating Center Director, as well as to the Data and Safety Monitoring Committee. Details of these procedures are addressed in the FPRC Handbook of Procedures.

#### **17.7.5. 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 checked. The data records identified as the sample are printed and checked against the PIFs. In addition, the photographs identified as present on the PIFs are checked against the photographs/CDs in the patient files. At the same time the labels on the photographs and CDs 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 FPRC Principal Investigator, FPRC Director, Coordinating Center Principal Investigator, and Coordinating Center Director. Details of these procedures are addressed in the FPRC Handbook of Procedures.

#### **17.7.6. Calibration Of Reader Workstations**

Calibration of the computer monitors used for grading is performed on a weekly basis (See 17.5.4).

### **17.8. STORAGE OF PHOTOGRAPHIC MATERIALS AND DOCUMENTATION**

Patient files will be established and maintained in order by CATT identification number. Filing cabinets with patient files will be locked when not in use. A patient file will contain digital images on CD-R's, color photographs when applicable, film based angiography when applicable, the CATT Image Data Submission Sheets, and completed grading forms. All materials are housed in a single location, 7th Floor, 3535 Market Street, Philadelphia. Badge identification is required to enter the building. In addition, a coded badge is required to access the FPRC.

### **17.9. DATABASE SECURITY**

Access to images and data will be password protected. Rights to specific files and images will be determined by the need for access. Only the Principal Investigator or Director can authorize access to the FPRC server and its databases.



The FPRC contracts with the School of Medicine Information Services (SOMIS) for server space and desktop support. This service includes server operating system administration, backup/recovery, 24/7 production support and backup. The Backups include disaster recovery, nightly backup with retrieval within 24-48 hours. Backups are stored offsite from the SOMIC server.

The server and all workstations will be protected with current virus protection software, including monthly, scheduled, virus protection updates.

#### **17.10. FPRC HANDBOOK OF PROCEDURES**

The FPRC Director, Principal Investigator and staff are responsible for developing a Handbook of Procedures as a reference document for the FPRC staff and for others interested in FPRC operations. The descriptions of procedures included in the Handbook are more detailed than those presented in the relevant chapters of this Study Manual of Procedures and give step by step instructions for each task required to carry out the responsibilities of the FPRC. The Handbook is updated regularly as minor refinements to procedures occur.

#### **17.11. FPRC STAFF MEETINGS**

The FPRC staff meets twice a month. The FPRC Principal Investigator is present at these meetings as needed. Members of the FPRC 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 18

### OCT READING CENTER OPERATIONS AND PROCEDURES

#### 18.1. RESPONSIBILITIES OF THE OCT READING CENTER

The OCT Reading Center at Duke University is responsible for receiving, inventorying, processing, storing, analyzing and archiving data of study patients imaged at the CATT clinical centers, and transmitting these data to the CATT Coordinating Center.

Duke will serve as the Optical Coherence Tomography (OCT) Reading Center to support the CATT Study. Duke will provide the necessary personnel, facilities, equipment and supplies required to perform the research, and will use best efforts to successfully complete the research, in accordance with all applicable legal and industry standards. The CATT OCT Reading Center will perform the following activities in CATT, unless directed otherwise by Coordinating Center:

- Provide advice to the Executive Committee on the analysis, interpretation and reporting of color optical coherence tomography images obtained from study sites;
- Provide OCT technicians with detailed written procedures for (i) performing OCT scans and (ii) transmitting images to the OCT Reading Center in accordance with the CATT study protocol;
- Certify clinical center OCT technicians in the above procedures;
- Review OCT scan quality and provide prompt feedback to OCT technicians as needed;
- Grade OCT scans from screening and follow-up visits;
- Monitor the quality and reproducibility of grading;
- Transmit grading data in electronic format to the CATT Coordinating Center promptly upon request.

The OCT Reading Center is responsible for gathering, organizing and analyzing data in a manner that is useful for scientific study and that meets all federal regulations for clinical trials.

#### 18.2. ORGANIZATION OF THE CATT OCT READING CENTER

Staffing may change as studies progress. The CATT OCT Reading Center staff includes:

- Director/PI
- Director of Grading Senior Technical Analyst
- Project Manager
- Administrative Coordinator/Data Coordinator
- Technical Analyst

- OCT Graders
- Financial Coordinator for Research at Duke
- Biostatistician
- Quality Assurance and Data Audit Team

*Advisory Group*

- Consultant for IRB and Regulatory Issues
- Duke Clinical Research Institute

### **18.2.1. Director/PI**

The Director is responsible for the overall performance of the CATT OCT Reading Center. Specific responsibilities are to:

- Ensure adequate infrastructure for proper performance of the OCT Reading Center activities;
- Prioritize the tasks of the OCT Reading Center;
- Chair meetings of OCT Reading Center Staff to identify and resolve problems in the implementation of OCT Reading Center projects;
- Collaborate with the Director of Grading, Senior Technical Analyst and Project Manager to develop, maintain, and refine grading program;
- Organize research efforts for publications involving OCT Reading Center methods
- Ensure that the CATT meets federal standards for clinical trials;
- Present at scientific meetings information regarding OCT image interpretation and grading;
- Continue IRB and HIPAA training;
- Participate in development and revisions of the OCT Manual Procedures (MOP).

### **18.2.2. Director of OCT Grading**

The Director of OCT Grading is responsible for OCT Reading Center grading protocol development and grader certification. Specific responsibilities are to:

- Direct the development, refinement, and maintenance of OCT grading protocols;
- Direct grading process quality improvement;
- Help to develop OCT Reading Center Grading certification protocols;
- Review and approve all OCT grader certification;
- Help to develop computer-assisted OCT scan grading tools;
- Participate in OCT Reading Center MOP refinement;

- Present at scientific meetings information regarding OCT image interpretation and grading;
- Coordinate with the CATT Fundus Photographic Reading Center to develop OCT scan protocols and grading protocols that will facilitate meaningful comparisons between OCT scan data and fundus photographic and fluorescein angiographic data;
- Continue IRB and HIPAA training;
- Approve all OCT Graders;
- Coordinate with the PI/Director on all Reading Center responsibilities listed under 18.2.1. above.

### **18.2.3. Senior Technical Analyst**

The Senior Technical Analyst is responsible for the technical day-to-day operations of the OCT Reading Center. Specific responsibilities of this role are to:

- Recruit, train, and supervise OCT Reading Center personnel;
- Design and execute OCT Graders' training program to ensure that adequately trained grading staff is available throughout the studies;
- Serve as a OCT Grader as needed, especially during the training and certification of the OCT Graders;
- Supervise training and certification of Coordinators and OCT Technicians for OCT data capture and submission to the OCT Reading Center;
- Maintain the OCT Reading Center Grading Manual;
- Collaborate with the OCT Reading Center Principal Investigator and Director to develop, maintain, and refine the grading protocol;
- Prepare presentations for Investigative Group and scientific forums;
- Assist with preparation of general OCT publications;
- Supervise certification procedures for OCT technicians;
- Communicate with clinical centers on issues of imaging/scanning performance;
- Assist with IRB grant continuation and renewals for review and approval by the Principal Investigator of each OCT Reading Center protocol;
- Continue IRB and HIPAA training.

### **18.2.4. Project Manager**

The Project Manager assists the Principal Investigator, Director, and Senior Technical Analyst with the administrative matters of the OCT Reading Center. Specific responsibilities are to:

- Organize and supervise daily operations;
- Communicate with other Study resource centers;

- Prepare communication for new study centers;
- Assist with training of Study Coordinators;
- Collaborate with the OCT Reading Center Director, PI, and Senior Technical Analyst to develop, maintain, and refine the OCT grading protocol;
- Prepare grant renewals and continuations for review and approval by the PI;
- Assist with recruitment and training of OCT Reading Center personnel;
- Serve as liaison between the OCT Reading Center and the CATT clinical centers;
- Establish and maintain status records of certifications of OCT technicians;
- Maintain budget and monthly reporting of expenditures;
- Assist with preparation of annual budget;
- Prepare templates of all OCT Reading Center forms and maintain record of all revisions;
- Participate in development of OCT Reading Center MOPs;
- Maintain budget and monthly reports;
- Continue IRB and HIPAA training;

#### **18.2.5. Administrative Coordinator/Data Coordinator**

The Administrative Coordinator/Data Coordinator assists the OCT Reading Center Director, Project Manager, Director of OCT Grading, and Sr. Technical Analyst with the administrative matters of the OCT Reading Center. Specific responsibilities are to:

- Organize and manage daily operations;
- Accession, inventory, track, and store all OCT materials received at the OCT Reading Center;
- Participate in development and maintenance of the OCT Reading Center MOP;
- Interact with the CATT clinical centers as necessary;
- Establish OCT Reading Center files as patients are enrolled into CATT;
- Prepare electronic data for the grading process;
- Process data entry of electronic grading and adjudication forms;
- Respond to data queries as appropriate;
- Order OCT Reading Center supplies;
- Maintain an inventory and obtain duplicate scans for internal use and teaching presentations;
- Prepare templates of all OCT Reading Center forms and maintain records of all revisions;
- Assist with word processing and graphics;

- Assist all OCT Reading Center staff as necessary to meet the needs of the study;
- Attend OCT Reading Center group meetings as needed;
- Ensure that all data received and handled meet applicable HIPAA standards;
- Assure all OCT Reading Center staff are in compliance with all regulatory agencies;
- Manage Vdata and Qdata;
- Prepare scans for QA cycles.

#### **18.2.6. Technical Analyst**

The Technical Analyst is responsible for assisting the Senior Technical Analyst. Specific responsibilities of this role are to:

- Assist with training and certification of Study Investigators, Coordinators, and OCT Technicians for OCT data capture and submission to reading center;
- Assist with maintaining the OCT Reading Center Grading Manual;
- Collaborate with the OCT Reading Center Principal Investigator and Director to develop, maintain, and refine the grading protocol;
- Assist with preparation of general OCT publications;
- Assist with certification procedures for OCT technicians;
- Communicate with Clinical Centers on issues of imaging/scanning performance;
- Perform OCT technician evaluations;
- Continue IRB and HIPAA training.

#### **18.2.7. OCT Graders**

The OCT Graders are responsible for the evaluation and grading of OCT scans according to the OCT Grading Manual. The specific responsibilities of the OCT Graders are to:

- Evaluate all visit scans according to OCT Reading Center protocols;
- Evaluate materials submitted for OCT technician certification according to OCT Reading Center protocols;
- Follow all masking requirements;
- Continue IRB and HIPAA training
- Provide feedback on errors or poor quality scans to Data Coordinator.

#### **18.2.8. Financial Research Coordinator for the Duke University Eye Center**

The Financial Research Coordinator will be responsible for first line financial administration of OCT Reading Center projects. She/he is accountable both to the PI for facilitating the orderly conduct of research and the appropriate academic and financial administrators for ensuring fiduciary compliance.

### 18.2.9. Biostatistician

The biostatistician provides expertise in data file creation, auditing, querying, updating and transfer. She/he will also analyze OCT data for reproducibility and provide status reports to the OCT Director. Specifically, she/he will:

- Decide size of sample for audit of OCT data files, based on anticipated error rate and margin of error;
- Randomly select patient data records and variables for audit;
- Develop system for tracking audit results: types of errors, corrections performed;
- Monitor version status of Excel files;
- Convert Excel files into SAS files;
- Develop queries for data quality;
- Generate computerized form for use in tracking query resolution;
- Maintain versions of SAS data files;
- Carry out statistical assessments of reproducibility within and between graders;
- Generate data tracking and quality assurance reports;
- Interact with the Duke Clinical Research Institute (DCRI) regarding transfer of digitally captured files for grading;
- Provide documentation of SAS data files.

### 18.2.10. Quality Assurance and Data Audit Team

The Quality Assurance and Data Audit Team comprises Research Analysts experienced in clinical trial data management and is responsible for confirming the accuracy of data entry; both the volumetric data and the qualitative (morphologic) grading data entered into a database via a custom web-based grading program (InForm™). Quality Assurance audits are performed on hardcopy printouts of complete databases. The Quality Assurance and Data Audit Team note discrepancies on printouts in red ink and return these for data-entry correction performed only by the Data Coordinator. The corrected data are reviewed, signed, and submitted to the Principal Investigator for release to the CATT Coordinating Center. Any data released, at the Coordinating Center's request, without going through a Quality Assurance audit will be marked as an *incomplete data set not yet audited for quality assurance*. Members of the Quality Assurance and Data Audit Team will:

- Perform Quality Assurance review for the data entry system;
- Perform Quality Assurance review for the grading system;
- Have NO involvement in data entry or management;
- Submit discrepancies to the Data Coordinator;
- Review corrected data

### **18.2.11. IRB Consultant**

The IRB Consultant is the Chief Clinical Research Coordinator for Duke University Eye Center and as such is responsible for review of IRB submissions for all clinical research projects. He/she provides consultation regarding University and Federal regulations that apply to the OCT Reading Center.

### **18.2.12. Duke Clinical Research Institute**

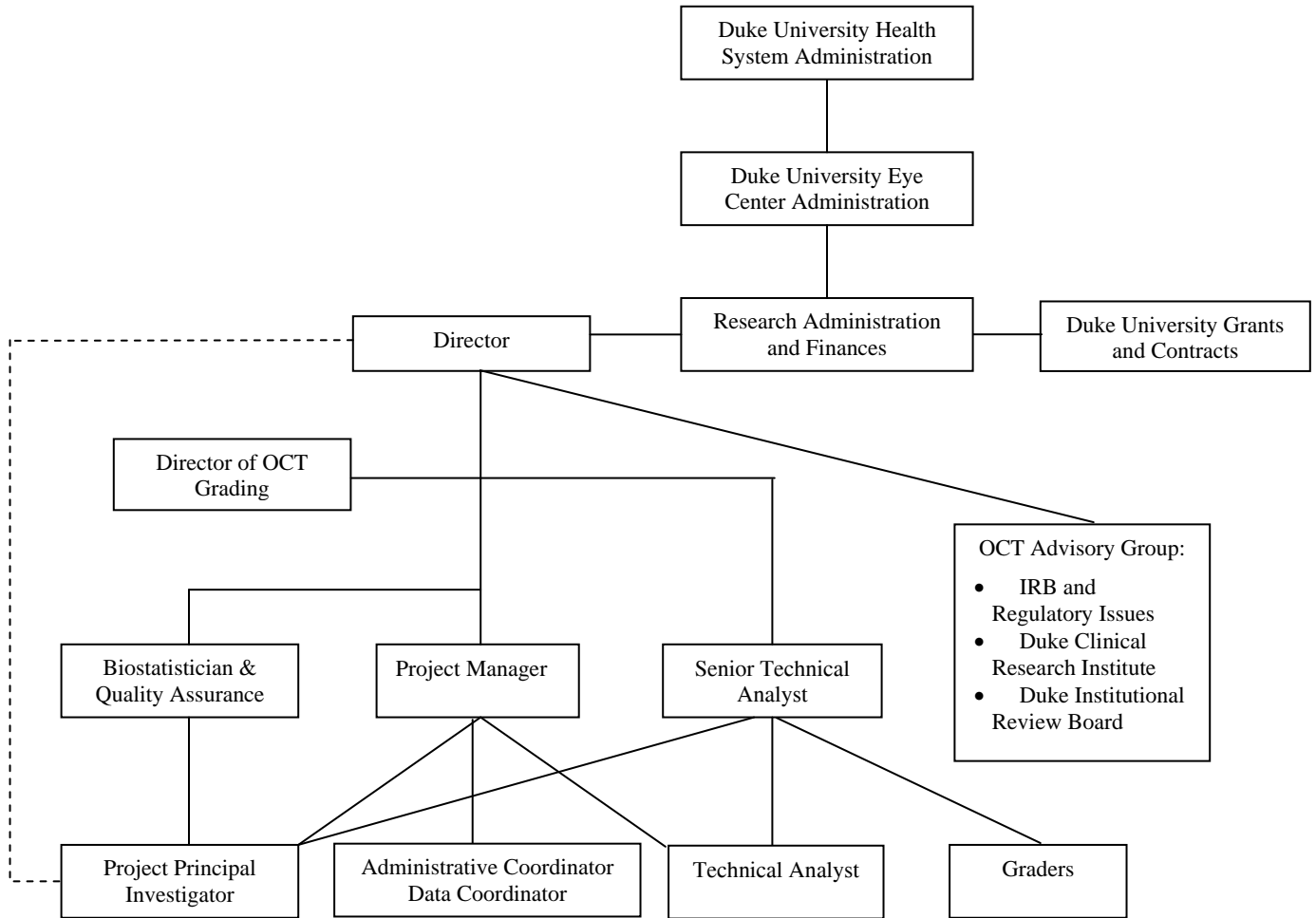
The Duke Clinical Research Institute (DCRI) offers a unique combination of clinical expertise, academic leadership, operational capabilities, and business acumen that translates into targeted and sound research results.

### **18.2.13. Duke Institutional Review Board**

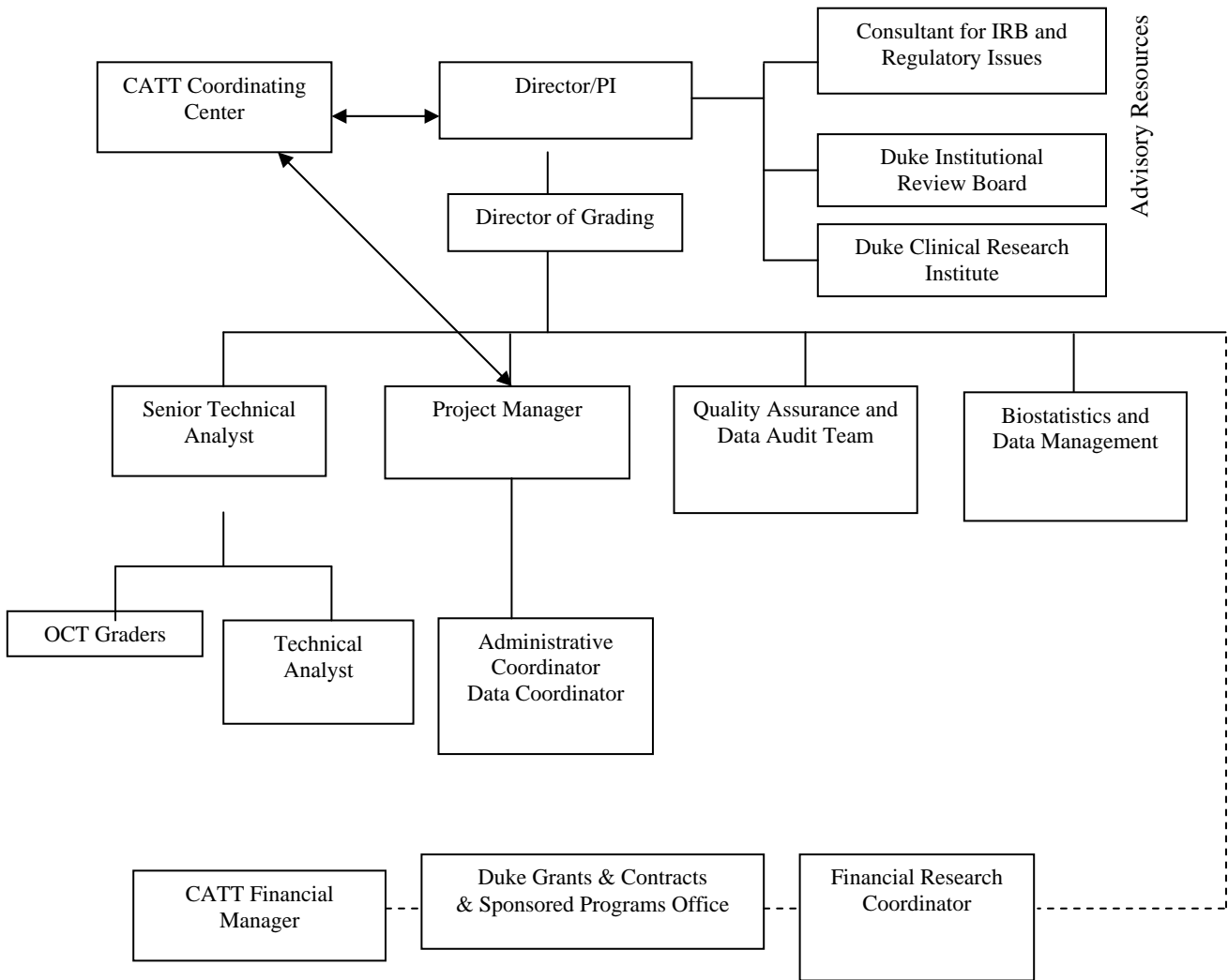
The Duke University Health System (DUHS) Institutional Review Board for Clinical Investigations (IRB) is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The DUHS IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the DUHS IRB complies with 45CFR46, 21CFR50, 21CFR56, 21CFR312, and 45CFR164.508-514. In addition, except where in conflict with 21CFR56, the DUHS IRB complies with the Guidelines of the International Conference on Harmonization.



# OCT READING CENTER Organizational Chart



# Organizational Chart For CATT Studies



### **18.3. CERTIFICATION & TRAINING OF STAFF, GRADERS & TECHNICIANS**

#### **18.3.1. Certification and Training of OCT Reading Center Personnel**

##### **18.3.1.1. Clinical Trial Certification**

To remain in compliance with standard Duke University and governmental regulatory practices, all OCT Reading Center personnel are certified for clinical trials through Duke IRB training modules. These training modules include basic education in research ethics. This certification includes both Good Clinical Practices and HIPAA training. All OCTRC staff are required to complete 2 research ethics modules upon hiring and then two modules annually.

The OCTRC staff attends continuing medical education lectures at Duke Eye Center, as they relate to eye imaging. OCTRC staff attends annual CATT Investigative Group Meetings. Various OCTRC staff attends the annual AAO meeting.

The OCTRC staff will review the OCTRC MOPs and a “MOP Reviewed/Signature” document will be kept in the individual’s staff file. This document is confirmation that the employee has received, reviewed and understands the procedures. The “MOP Reviewed/Signature” document will include the employee’s signature and the Director of the OCT Reading Center’s signature.

##### **18.3.1.2. Quarterly Review**

The Director/PI will lead meetings of the OCT Reading Center staff. The purpose of these staff meetings is to ensure the execution of the procedures set forth in the *OCT Reading Center MOPs*, identify problems with implementation of the study protocol either within the Reading Center or study sites, formulate plans for the resolution of problems, and to set goals for productivity.

#### **18.3.2. Certification and Training of OCT Graders**

OCT Graders for the OCT Reading Center will be certified once they have completed the appropriate Grader Knowledge Assessment Questionnaire and demonstrated a thorough understanding of the grading system. Standard procedures are in place to reinforce quality grading and to prevent unacceptable degrees of intra-grader variability. For certification, OCT graders will read 10 sets of scans. Grades are reviewed and approved by the Director of OCT Grading and Sr. Technical Analyst. All Graders must be approved for grading by the Director of Grading before grading actual study scans/data.

#### **18.4. Certification and Training of OCT Technicians**

The OCT Reading Center will educate and certify Study OCT technicians to obtain quality scans and consistent measurements of study patients utilizing OCT images and quantitative data. The OCT Reading Center will provide OCT technicians with detailed written procedures for taking high quality tomographs. A certification approval will be kept on file in alphabetical order at the OCT Reading Center. Verification of certification will be emailed to the Clinic Coordinator and Technician and followed up with a paper copy letter to be filed at the Clinical Center. We will modify our certification protocols as equipment and software

change. We will keep records of all protocol changes (see Section 14.9 of this manual for detailed information about the certification of CATT OCT Technicians).

## **18.5. MATERIAL COLLECTION FROM CLINICAL SITES AND PROCESSING**

The OCT Reading Center will provide the CATT Clinical Centers detailed written procedures for transmitting images to the OCT Reading Center at Duke in accordance with the study protocol. The following procedures are the responsibility of the OCT Reading Center.

### **18.5.1. OCT Image Identification**

Detailed instructions are provided for labeling the OCT scans with the patient's study ID number, alpha code and visit identifier. Study coordinators are instructed NOT to provide patient identifiers as established by HIPAA guidelines (see below) on any materials submitted to the OCT Reading Center. In the event that this occurs, the materials will not be accepted and the clinical center must resubmit the OCT scans without the patient's identifiers.

All OCTs must be masked and/or de-identified. The OCT Reading Center will follow HIPAA regulations for de-identifiers.

#### HIPAA De-Identification List:

- Name
- Address
- Telephone Numbers
- Fax Numbers
- Electronic mail addresses
- Social Security Numbers
- Medical Record Numbers
- Health plan beneficiary number
- Account numbers
- Certificate/license number
- Vehicle identifiers and serial numbers
- Web Universal Resource Locators (URL)
- Internet Protocol (IP) address numbers
- Biometric identifiers
- Full face photographic images
- Any other unique identifying number, characteristic or code

Whenever there are missing scans, missing information, mislabeled scans or other discrepancies regarding the scan materials, the OCT Reading Center Project Manager or Data Coordinator will fax a list of discrepancies to the Clinic Coordinator. OCT scans are not presented to the graders until all problems or discrepancies are resolved. Unmasked OCTs or OCTs with identifiers will not be accepted.

### **18.5.2. Receipt of OCT Images at the OCT Reading Center**

The Data Transmission Site (DTS) is administered by the OCT Reading Center Project Manager and Data Coordinator. The DTS is configured along with the Stratus OCT clinical trial module to minimize errors in labeling and transmission. All data are received at the DTS

in uncompressed, zipped files. Upon receipt, the Project Manager/Data Coordinator unzips each file submission and checks the entry for accuracy and completeness and resolves any discrepancies before scans are accepted and assigned to graders. Once the Project Manager/Data Coordinator accepts the scans as “grade ready”, they are entered into a “received scans” database. If the scans are not “grade ready” due to missing data or other discrepancy, they are entered into a “received-rejected” database and the site is contacted to resolve the problem. In some cases, incomplete data submissions are acceptable and graded instead of skipping the visit completely.

## **18.6. OCT GRADING AND FEEDBACK**

The OCT Reading Center will grade images from study visits according to industry standard optical coherence tomography reading procedures. Also, the OCT Reading Center is responsible for monitoring reproducibility of grading.

### **18.6.1. Access and Viewing of OCT Images**

OCT images will have already been labeled with the patient study ID number, alpha code and visit identifier so that this information may be crosschecked with the grading form. Any discrepancies are brought to the attention of the OCT Reading Center Data Coordinator and resolved. The Data Coordinator will not give Graders multiple scans from the same patient to grade on the same day. Aside from viewing and measurement, the OCT Grader will not be permitted to enhance or otherwise alter the original image in any way.

### **18.6.2. General Grading Procedures**

The Grader verifies that the patient information on the OCT scan matches the patient information on the grading form. Discrepancies found by the Grader are submitted to the Data Coordinator and are resolved. The Data Coordinator will assign each scan to two Graders. Each grader reads the OCT scans and notes his/her answers on the CATT grade sheet. The grade sheets are reviewed and like answers are transcribed to an arbitration grade sheet. A senior grader (arbitrator) reads the OCT scan and resolves discrepancies or the two original graders openly discuss and resolve (adjudicate) the areas of disagreement. If graders cannot reach agreement, the Director of Grading assists the graders in reaching a consensus. The final grade is submitted to a staff specialist for data entry.

The grading staff meets monthly. Grading issues and unresolved adjudication by the OCT Graders will be reviewed and discussed with the Senior Technical Analyst.

OCT grading procedures are uniform throughout all visits of the study. Baseline eligibility or exclusion is determined with fundus photograph and angiographic images, not by OCT criteria. A given set of scans is graded with an online electronic grading form subdivided into three major sections; volumetric, morphologic, and scan measurements.

The first grading section is the “**Volumetric Map Quality**” section. Using OCT analysis software, a retinal map scan set is assessed to determine if the volumetric values were obtained correctly as the software may fail to accurately recognize the inner and outer retinal layers used to compute accurate thickness values.

Volumetric quality grading is based on the following criteria:

- Presence of “gross errors” on any of the 6 radial scans of a retinal map
- Presence of “minor errors” on any of the 6 radial scans of a retinal map
- Presence of any errors in the Central Map, 1mm section of a retinal map

The second grading section is the “**Presence and Grading of Components**” which assesses the morphologic components of all of the line scans obtained in a study visit. Morphologic grading is based on the following criteria:

- Macular edema: (yes/no)
- Foveal edema: (yes/no)
- Cystic edema: (yes/no)
- Single or multiple cysts: (yes/no)
- Size of cysts: enter value
- Subretinal fluid: (yes/no)
- Foveal subretinal fluid: (yes/no)
- Posterior vitreous visible: (yes/no)
- Vitreomacular attachment (VMA): (yes/no)
- Fovea deformed at VMA: (yes/no)
- Epiretinal membrane (ERM): (yes/no)
- Fovea deformed at ERM: (yes/no)
- Retinal pigment epithelium elevation (RPEE): (yes/no)
- Single RPEE: (yes/no)
- Width of RPEE: enter value
- Height of RPEE: enter value
- Foveal RPEE: (yes/no)
- Choroidal neovascularization (CNV): (yes/no)
- Width of CNV: enter value
- Foveal CNV: (yes/no)
- Well defined CNV: (yes/no)
- Dense highly reflective CNV: (yes/no)
- Subretinal Hemorrhage: (yes/no)

The third and final grading section is the “**OCT Scan Measurement**” section. In this section, the grader determines quantitatively (with electronic calipers) the retina, choroidal neovascularization, retinal pigment epithelial elevations and subretinal fluid thickness, measured at the fovea on all line scans obtained in a study visit. These grader-determined values are especially important as the OCT retinal map software frequently cannot clearly identify the inner and outer retina in the presence of choroidal neovascularization. Also, retinal thickness measurements obtained manually may provide more accurate thickness data when computed retinal map values are determined to be of little or no value in the first grading section, “**Volumetric Map Quality**”.

### **18.6.3. Feedback**

The OCT Reading Center reviews each study submission and assigns a quality rating. The Technical Analyst provides prompt feedback to the Clinical Center via phone, email, or letter as needed. The Graders will confirm whether the images received for grading are usable. At regular intervals (determined by the CATT Coordinating Center) the OCT Reading Center will provide the CATT Coordinating Center with summary reports to document individual OCT Technician and study site performance.

## **18.7. DATA ENTRY AND DATA MANAGEMENT**

The OCT Reading Center will collect data from retinal maps and scans of patients enrolled in CATT utilizing OCT technology.

### **18.7.1. Data Entry of OCT V**

Scans are inventoried upon receipt and the V-data (printed volumetric data from the OCT Map) is entered into a Microsoft Excel spreadsheet. The data files are archived on the DCRI Oracle server, and backed up daily. Once the Data Coordinator has reviewed the scans and has verified that they meet the OCT Reading Center's protocol, the scans are released to the graders for analysis.

### **18.7.2. Preparation of Grading Forms**

The OCT Reading Center Data Coordinator assigns OCT scans after she has verified that the scans are ready for grading.

### **18.7.3. Data Entry of Qualitative Data (Q-data)**

OCT RC staff specialist enters Qualitative data from final grade sheets onto an Excel Spreadsheet. The Excel files are sent electronically to the Project Manager for review before printing and auditing. After reviewing spreadsheets, the Project Manager prints the file. Then the auditor compares each final grade sheet to data on spreadsheet (100%), notes errors on the printout, and returns to the Project Manager. After the Project Manager makes corrections, the file is sent electronically to the Coordinating Center and printouts are archived at offsite storage facility.

### **18.7.4. Backup Schedule**

The Data collected at the OCT Reading Center will be stored at the DCRI on a secure file server network. To ensure the OCT Reading Center data is not lost to fire, computer malfunction, etc., all Reading Center data will be backed up weekly.

### **18.7.5. Security**

The OCT Reading Center databases are protected by operating system passwords, application-level passwords, or both. The OCT Reading Center computer can only be accessed with a password because a password enabled screensaver is engaged at all times. The single entry door to the Reading Center is locked at all times. Only OCT Reading Center staff have permission to access or modify those sectors of the database and data management

system that pertain to his or her assigned responsibilities. The OCT Reading Center staff is regularly advised of the precautions that should be taken and the potential consequences of a security breach. Commonly accepted password security procedures, such as regular changes, are practiced.

## **18.8. DATA ANALYSIS AND REPORTING**

The OCT Reading Center will provide advice to the Coordinating Center on the analysis, interpretation and reporting of color optical coherence tomographs related to the study. Data and reports will be transmitted to the study sponsor in electronic format upon request.

### **18.8.1. Reporting Data**

The OCT Reading Center at Duke will transfer the data to the Coordinating Center in a secure manner, via the OCT Reading Center electronic data transfer system. The transmitted data will comprise the spreadsheets for the V-data, the Q-data, the variable definitions for V-data and the variable definitions for Q-data and a cover letter. The cover letter will include the number of study sites included in the report, the number of patients included and the number of OCT scans received and entered for this report. We will note any unusual data and the Director/PI will sign the cover letter.

### **18.8.2. Data Analysis**

Although the OCT Reading Center will provide advice to the CATT Coordinating Center on the analysis and interpretation of data we will not directly analyze the data. OCT Reading Center personnel can publish or present data from these studies with the permission of the CATT Executive Committee and DSMC.

### **18.8.3. Progress Reports**

The OCT Reading Center will provide periodic progress reports to the CATT Study Chair and Executive Committee. The reports will be submitted according to timelines and formats as required. The Director/PI will approve all progress reports prior to submission to the study sponsor.

## **18.9. SYSTEM INSTALLATION, CALIBRATION & MAINTENANCE**

### **18.9.1. System Installation**

All computer systems are purchased directly from the computer manufacturer or Carl Zeiss-Meditec and installed by Duke Eye Center's Information Technology (IT) personnel. Most PCs run on the Windows XP operating system and are linked via the Eye Center high-speed network. Internet transmissions are made via high speed T1 connection.

### **18.9.2. System Calibration**

Stratus OCT systems at each Clinical Center are installed, maintained and calibrated by authorized Carl Zeiss-Meditec service technicians only. Periodic system calibration is performed at every service visit and recommended at least annually (hardcopy reports of such calibrations will be generated by each machine in the near future based upon calibration of a "test eye" developed by Carl Zeiss Meditec in association with the OCTRC). The grading



software's *reproducibility of analysis* (Stratus Reader) is routinely validated by a module developed by the OCT Reading Center's Statistician/Quality Assurance representative.

### **18.9.3. System Maintenance**

Periodic and routine maintenance is conducted by both Reading Center and Duke Eye Center IT personnel. Passwords are changed on a routine basis at predetermined intervals. All systems are protected from viruses and spy ware by the Eye Center network administrator firewall system. All systems are shut down at night and are password protected upon start up. No software upgrades are to be made to any site's Stratus OCT without authorization of the OCTRC during the duration of the CATT.

### **18.9.4. Software Validation**

We require an OCT Technician from each clinical center to submit yearly printouts for system and software validation at each site. These printouts are correlated with scan data reproduced on our software to check "accuracy of reproduction."

The percentage of scans with reading errors caused by software will be determined by taking a random sample of the scans and ascertaining whether the software produces the same readings on a second scan. The level of accuracy (margin of error) for the estimated error rate must first be determined. For example, if the estimated error is 25% and there is a margin of error of 5%, then the percentage of records having errors in the whole data set is sure to be between 20 and 30. The number of records to audit can be determined by using the following formula:

$$\text{Number of records} = [ 4 \times (\text{percent with error}) \times (\text{percent without error}) ] / (\text{margin of error})^2$$

The number of scans to be audited will be based on whichever estimate of the error expected is most appropriate and for the margin of error desired. The number of scans currently in the database will be obtained. Then, a computer program will be used to select a random sample from the total database that corresponds to the number of scans to be audited. The scans to be audited will be numbered sequentially and linked with the actual ID numbers of the scans. The OCT images in these scans will be read a second time. The number of errors will be recorded. An error will occur if any of the 9 areas of the scan are discrepant on a second reading. In addition, the value of the foveal thickness will be compared for each pair of scans. If this number is different, then an error will be declared. Then the percentage of errors that occurred in the sample, as determined by these two measures, will be computed.

## **18.10. QUALITY ASSURANCE**

The purpose of the quality assurance activities of the OCT Reading Center is to ensure the integrity and completeness of the data collected from the evaluation of the scans. These activities include the following:

- Mask Graders to treatment assignment
- Test reproducibility of Grading protocol
- Confirm data entry accuracy
- Confirm accuracy of OCT materials and their labels.

### **18.10.1. Masking OCT Graders to Treatment Assignment**

None of the materials submitted to the OCT Reading Center will indicate to which treatment group the patient was randomized. The purpose of this is to remove any bias that may be introduced on the part of the Graders by knowing the treatment assignment. All other identifying data on the scan is masked including treatment type.

### **18.10.2. Reproducibility Test of Grading Protocol**

The purpose of the Quality Assurance (QA) system is to measure reproducibility of the grading scheme, reproducibility of the OCT Graders, and to monitor for Grader drift. A predetermined set of scans will be re-graded by each Grader at specified times. Five percent of scans will be re-graded, and re-adjudicated. The results of the QA system identify agreement between Graders as well as the reproducibility of each Grader.

The OCT Reading Center Senior Technical Analyst and Principal Investigator will review the results of the QA gradings with the OCT Graders. In addition to the re-grading of the QA set of scans, grading issues are identified on a regular basis and discussed with the OCT Graders.

### **18.10.3. Inter- and Intra-grader reliability checks**

The assessment of reliability will be carried out using several methods. For continuous variables, inter- and intra-grader agreement will be assessed using the intraclass correlation. A value of 0.9 or greater will indicate almost perfect agreement. For categorical variables, a kappa statistic and a McNemar's test will be carried out to determine agreement either within or between graders.

## **18.11. REGULATORY COMPLIANCE, INSPECTIONS, AUDITS AND CLOSEOUT**

### **18.11.1. Regulatory Compliance**

The OCT Reading Center at Duke will provide the necessary personnel, facilities, equipment and supplies required to perform the research, and will use best efforts to successfully complete the research, in accordance with all applicable legal and industry standards. All studies performed at the OCTRC have IRB approval through the Duke University Institutional Review Board. The data handling and management of this study will be carried out under Good Clinical Practice/Health Insurance Portability and Accountability Act (HIPAA) guidelines for maximum assured confidentiality. The CATT Coordinating Center will ensure that informed consent was obtained from the study participants. Therefore, the OCT Reading Center is not responsible for informed consent.

### **18.11.2. Study Closeout**

The OCT Reading Center at Duke will retain the results of the study during the term of NEI sponsorship, and for six years thereafter, unless and until the NIH provides written permission to dispose of or deliver the same. The OCT Reading Center will follow all Duke University Medical Center and federal regulations for study closeout.

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