# Diabetic Retinopathy Clinical Research Network

# A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema

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## 1.1 Background and Rationale

### 1.1.1 Background Information on Diabetic Macular Edema

Diabetic retinopathy is a major cause of visual impairment in the United States.[1-3] Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) estimate that after 15 years of known diabetes, the prevalence of diabetic macular edema is approximately 20% in patients with type 1 diabetes mellitus (DM), 25% in patients with type 2 DM who are taking insulin, and 14% in patients with type 2 DM who do not take insulin.[1]

In a review of three early studies concerning the natural history of diabetic macular edema, Ferris and Patz found that 53% of 135 eyes with diabetic macular edema, presumably all involving the center of the macula, lost two or more lines of visual acuity over a two year period.[4] In the Early Treatment Diabetic Retinopathy Study (ETDRS), 33% of 221 untreated eyes available for follow-up at the 3-year visit, all with edema involving the center of the macula at baseline, had experienced a 15 or more letter decrease in visual acuity score (equivalent to a doubling of the visual angle, e.g., 20/25 to 20/50, and termed "moderate visual loss").[5]

In the ETDRS, focal/grid photocoagulation of eyes with clinically significant macular edema (CSME) reduced the risk of moderate visual loss by approximately 50% (from 24% to 12%, three years after initiation of treatment).[6] Therefore, 12% of treated eyes developed moderate visual loss in spite of treatment. Furthermore, approximately 40% of treated eyes that had retinal thickening involving the center of the macula at baseline still had thickening involving the center at 12 months, as did 25% of treated eyes at 36 months.[7]

Although several treatment modalities are currently under investigation, the only demonstrated means to reduce the risk of vision loss from diabetic macular edema are laser photocoagulation, as demonstrated by the ETDRS, and intensive glycemic control, as demonstrated by the Diabetes Control and Complications Trial (DCCT)[8] and the United Kingdom Prospective Diabetes Study (UKPDS).[9] In the DCCT, intensive glucose control reduced the risk of onset of diabetic macular edema by 23% compared with conventional treatment. Long-term follow-up of patients in the DCCT show a sustained effect of intensive glucose control, with a 58% risk reduction in the development of diabetic macular edema for the DCCT patients followed in the Epidemiology of Diabetes Interventions and Complications Study.[10]

The frequency of an unsatisfactory outcome following laser photocoagulation in some eyes with diabetic macular edema has prompted interest in other treatment modalities. One such treatment is pars plana vitrectomy.[11-16] These studies suggest that vitreomacular traction, or the vitreous itself, may play a role in increased retinal vascular permeability. Removal of the vitreous or relief of mechanical traction with vitrectomy and membrane stripping may be followed by substantial resolution of macular edema and corresponding improvement in visual acuity. However, this treatment may be applicable only to a specific subset of eyes with diabetic macular edema. It also requires a complex surgical intervention with its inherent risks, recovery time, and expense. Other treatment modalities such as pharmacologic therapy with oral protein kinase C inhibitors and antibodies targeted at vascular endothelial growth factor (VEGF) are under investigation. The use of intravitreal corticosteroids is another treatment modality that has generated recent interest.

### 1.1.2 Rationale for Intravitreal Steroid Treatment: Mechanisms for Potential Efficacy

Diabetic macular edema results from abnormal leakage of macromolecules, such as lipoproteins, from retinal capillaries into the extravascular space followed by an oncotic influx of water into the extravascular space.[4] Abnormalities in the retinal pigment epithelium may also cause or contribute to diabetic macular edema. These abnormalities may allow increased fluid from the choriocapillaries to enter the retina or they may decrease the normal efflux of fluid from the retina to the choriocapillaris.[4] The mechanism of breakdown of the blood retina barrier at the level of the retinal capillaries and the retinal pigment epithelium may be due to changes to tight junction proteins such as occludin.[17]

The increase in retinal capillary permeability and subsequent retinal edema may be the result of a breakdown of the blood retina barrier mediated in part by VEGF, a 45 kD glycoprotein.[18] Aiello et al, demonstrated in an in vivo model that VEGF can increase vascular permeability.[18] Fifteen eyes of 15 albino Sprague-Dawley rats received an intravitreal injection of VEGF. The effect of intravitreal administration of VEGF on retinal vascular permeability was assessed by vitreous fluorophotometry. In all 15 eyes receiving an intravitreal injection of VEGF, a statistically significant increase in vitreous fluorescein leakage was recorded. In contrast, control eyes, which were fellow eyes injected with vehicle alone, did not demonstrate a statistically significant increase in vitreous fluorescein leakage. Vitreous fluorescein leakage in eyes injected with VEGF attained a maximum of 227% of control levels. Antonetti et al., demonstrated that VEGF may regulate vessel permeability by increasing phosphorylation of tight junction proteins such as occludin and zonula occluden 1.[19] Sprague-Dawley rats were given intravitreal injections of VEGF and changes in tight junction proteins were observed through Western blot analysis. Treatment with alkaline phosphatase revealed that these changes were caused by a change in phosphorylation of tight junction proteins. This model provides, at the molecular level, a potential mechanism for VEGF-mediated vascular permeability in the eye. Similarly, in human non-ocular disease states such as ascites, VEGF has been characterized as a potent vascular permeability factor (VPF).[20]

The normal human retina contains little or no VEGF; however, hypoxia causes upregulation of VEGF production.[21] Vinores et al, using immunohistochemical staining for VEGF, demonstrated that increased VEGF staining was found in retinal neurons and retinal pigment epithelium in human eyes with diabetic retinopathy.[21]

As the above discussion suggests, attenuation of the effects of VEGF provides a rationale for treatment of macular edema associated with diabetic retinopathy. Corticosteroids, a class of substances with anti-inflammatory properties, have been demonstrated to inhibit the expression of the VEGF gene.[22] In a study by Nauck et al, the platelet-derived growth-factor (PDGF) induced expression of the VEGF gene in cultures of human aortic vascular smooth muscle cells was abolished by corticosteroids in a dose-dependent manner.[22] A separate study by Nauck et al demonstrated that corticosteroids abolished the induction of VEGF by the pro-inflammatory mediators PDGF and platelet-activating factor (PAF) in a time and dose-dependent manner.[23] This study was performed using primary cultures of human pulmonary fibroblasts and pulmonary vascular smooth muscle cells.

Intravitreal injection has been proposed as a way to deliver corticosteroid (triamcinolone acetonide) to the posterior segment. Triamcinolone acetonide is a readily available pharmacologic agent (Kenalog® 40, Bristol-Myers-Squibb, Princeton NJ). However, it is not specifically formulated for intraocular use. The most common dose of triamcinolone acetonide used to treat eyes with diabetic macular edema is 4mg.[24] This dose is typically used because at a shelf dosage of 40mg/cc, it is

easily aliquoted to a 4mg/0.1cc dose. A volume of 0.1cc is readily injected into the vitreous cavity. Other than the convenience of this dose, there are no data that support the use of 4mg over any other alternative dose. The use of 25mg of triamcinolone acetonide has less commonly been used to treat eyes with diabetic macular edema.[25] However, there are no data that compare the efficacy and safety of the 4mg vs. the 25mg dose.

As discussed above, corticosteroids have been experimentally shown to down regulate VEGF production and possibly reduce breakdown of the blood-retinal barrier. Similarly, steroids have anti-angiogenic properties possibly due to attenuation of the effects of VEGF.[26, 27] Both of these steroid effects have been utilized. For example, triamcinolone acetonide is often used clinically as a periocular injection for the treatment of cystoid macular edema (CME) secondary to uveitis or as a result of intraocular surgery.[28, 29] In animal studies, intravitreal triamcinolone acetonide has been used in the prevention of proliferative vitreoretinopathy[30, 31] and retinal neovascularization.[32, 33] Intravitreal triamcinolone acetonide has been used clinically in the treatment of proliferative vitreoretinopathy[34] and choroidal neovascularization.[35-37]

### 1.1.3 Potential Adverse Effects of Intravitreal Corticosteroids

#### 1.1.3.1 Elevation of Intraocular Pressure

Intraocular pressure depends on the comparative rates of aqueous production and aqueous drainage, primarily through the trabecular meshwork. Increased intraocular pressure occurs from a variety of mechanisms such as primary or secondary angle-closure glaucoma, primary or secondary open-angle glaucoma, or combined-mechanism glaucoma. If inadequately treated, increased intraocular pressure may result in glaucomatous optic nerve changes and loss of visual field.

Among the secondary open-angle glaucomas, corticosteroid-induced elevation of intraocular pressure is one of the most common. This relationship is well established. In patients susceptible to this phenomenon, the elevation of intraocular pressure may occur as a result of topical, systemic, or peribulbar administration. For example, following 4 to 6 weeks of topical corticosteroid administration, 5% of subjects may show an elevation in intraocular pressure of >16 mmHg and 30% of subjects may show an elevation of 6 to 15 mmHg.[38, 39]

The mechanism of corticosteroid-induced elevation of intraocular pressure is incompletely understood. Possible theories include: a) inhibition of the production of outflow-enhancing prostaglandins, b) suppression of trabecular meshwork endothelial cell phagocytosis, c) increased deposition of proteoglycans or glycosaminoglycans in the trabecular meshwork with a resultant increase in resistance to outflow, d) increase in cross-linked actin networks in the trabecular meshwork, e) increase in the expression of cellular tight-junction protein, and f) stabilization of lysosomes which allow accumulation of hyaluronate or other debris in the trabecular meshwork.[40]

The intravitreal administration of corticosteroid is expected to be associated with an increased risk of elevated intraocular pressure in susceptible patients. The time course for the development of corticosteroid-induced elevation in intraocular pressure as a result of intravitreal injection is presently unknown. Additionally, the effect of the initial dose administered, the frequency of re-injection, or the cumulative dose administered over time on the severity of intraocular pressure elevation is not known. The experience thus far indicates that the 4mg and 25mg doses of triamcinolone acetonide appear to result in a relatively similar frequency and severity of intraocular pressure elevation.[24, 41] Re-injection of the 4mg dose at a frequency of more than once every 4 months appears to be associated with more frequent and more severe elevation in intraocular pressure.[35]

### 1.1.3.2 Cataract Formation

An opacity of the lens that results in loss of transparency and/or causes light scatter is called a cataract. The reasons cataractous changes develop include: formation of opaque fibers, fibrous metaplasia, epithelial opacification, accumulation of pigment and formation of extracellular materials. These changes can occur as a result of the aging process, trauma, radiation, electric shock, in association with systemic disorders, or as a result of drugs or chemicals. The most common types of cataract are cortical, nuclear, and posterior subcapsular.[42] In cortical cataracts, the soluble protein content decreases and results in lens alteration. Nuclear cataracts may form as a result of an increase in insoluble protein content along with the accumulation of chromophores. Posterior subcapsular cataracts are caused by dysplastic changes in germinal epithelium. These dysplastic cells migrate posteriorly and give rise to bladder cells of Wedl, resulting in posterior subcapsular opacity.

Among the toxic causes of cataract, corticosteroid-induced cataract is one of the most common. The relationship between dose and duration of exposure to the formation of cataract is unclear. However, the association between corticosteroids and cataract is well established. Corticosteroid-induced cataracts typically show an axial, posterior subcapsular opacity, which gradually increases in size. Nuclear sclerosis is not a typical lens change from corticosteroids. Topical, systemic and peribulbar corticosteroid administration have all been associated with an increased risk of cataract formation.[43] Even the prolonged administration of inhaled corticosteroids has been associated with an increased risk of cataract formation.[44]

The intravitreal administration of corticosteroid is also expected to be associated with cataract formation. The time course for the development of cataract as a result of intravitreal corticosteroid injection is presently unknown. However, it is believed that the formation of cataract in response to intravitreal administration is gradual and takes place over the course of approximately one year. As with other routes of corticosteroid administration, posterior subcapsular cataract appears to be the most common type of cataract to form following the intravitreal administration of corticosteroid.

### 1.1.3.3 Endophthalmitis

Endophthalmitis is an intraocular inflammatory process. It can be due to infection with pathogens such as bacteria of fungi or can be noninfectious. Clinical features include lid edema, conjunctival injection, corneal edema, anterior chamber and vitreous inflammation, and hypopyon. Infectious endophthalmitis can occur following an intraocular procedure (i.e., cataract surgery, vitrectomy surgery, intravitreal injection), as a result of systemic infection, as a result of trauma, or as a late feature of conjunctival filtering blebs. Acute post-operative endophthalmitis following cataract surgery is the most common cause. The overall incidence, however, is low and in one survey the incidence following cataract surgery was <1%.[45] In the Endophthalmitis Vitrectomy Study (EVS), gram-positive organisms accounted for 94% of culture-positive cases.[46]

The incidence and causative pathogens following intravitreal injection of corticosteroid are less well defined. At least in the published literature, this complication appears uncommon (Table 2). Endophthalmitis following repeated intravitreal injection of antiviral agents for the treatment of CMV retinitis also appears to be uncommon (personal communication, Daniel F. Martin). However, the injection of a bolus of medication such as corticosteroid that has immunosuppressive properties could theoretically result in a higher incidence of post-injection infectious endophthalmitis.

The clinical experience with intravitreal steroid injections to date has been with the use of Kenalog. Kenalog is a commercially available preparation that is FDA labeled for intramuscular or intrabursal use. The available preparation of Kenalog contains, in addition to triamcinolone acetonide, 0.99% benzyl alcohol, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80.[47] Cases of noninfectious endophthalmitis have been reported to be associated with intravitreal Kenalog injections, presumably related to the preservatives in the Kenalog preparation.[48, 49] Although the published literature to date on this complication is limited, anecdotal experience suggests that the incidence, though low, is meaningful (American Society of Retinal Specialists listserv from 2002-2004). As a result of the possibility of a sterile reaction to the components of the Kenalog vehicle, when intraocular inflammation develops following an intravitreal steroid injection, it is difficult to be certain if the inflammatory reaction is infectious or non-infectious. Treatment of infectious endophthalmitis requires immediate treatment with intravitreal antibiotics with or without vitrectomy surgery, depending on the clinical situation, whereas non-infectious endophthalmitis is usually self-limiting. For this reason, a sterile, preservative-free triamcinolone preparation will be used in this study.

### 1.1.4 Animal Studies

Intravitreal injection of triamcinolone acetonide and its vehicle has been shown to be non-toxic in animal studies.[47, 50] McCuen et al injected 1mg of pure triamcinolone acetonide into the vitreous cavity of 21 rabbit eyes.[50] Throughout the 3 month course of follow-up ophthalmoscopy, intraocular pressure, electroretinography (scotopic and photopic responses), and light and electron microscopy all remained normal. Hida et al evaluated the vehicle in the commercially available preparation of triamcinolone acetonide for potential toxicity.[47] At both the standard concentration and at twice the standard concentration (volume of 0.1cc), the Kenalog vehicle was demonstrated to be non-toxic in rabbit eyes. All eyes were followed for 14 days; following intravitreal injection there was no clinical evidence of damage to the lens or retina. Histologic evaluation demonstrated that there was no ultrastructural damage to the retina.

### 1.1.5 Clinical Studies (published series)

#### 1.1.5.1 Efficacy

Despite the extensive use of intravitreal corticosteroids in the last few years (thousands of eyes treated), published data are limited. There have been no published controlled trials of intravitreal corticosteroids for DME. Three case series have been published (Table 1).

**Table 1: Efficacy of Intravitreal Steroids for DME - clinical studies (published studies)**

| | # eyes treated | Dose (mg) | Anatomical improvement | Mean baseline visual acuity | Mean visual acuity at endpoint | Follow-up (mo) |
|---|---|---|---|---|---|---|
| Martidis[24] | 16 | 4 | 11/16 (69%)[1] | 20/200 | 20/80 | 3 |
| Jonas[41] | 26 | 25 | 21/21 had less leakage (FA) | 20/165 | 20/105 | 6.6 |
| Massin[51] | 15 | 4 | 12/12 had reduced central macular thickness | 48 letters | 53 letters | 3 |

1 - mean baseline OCT=540um, mean OCT at 3 months=224um

**Martidis et al**

Martidis et al reported results using intravitreal triamcinolone acetonide injection (4mg/0.1cc) in 16 eyes with macular edema due to diabetic retinopathy.[24] All 16 eyes had persistent macular edema

involving the center of the macula after having received 2 to 6 sessions of focal/grid laser photocoagulation. In 11 eyes with a known time of onset of macular edema, the average duration of macular edema was 32 months (range 13 to 68 months) prior to intravitreal triamcinolone acetonide injection. The other 5 eyes were known to have macular edema for at least 6 months. All 16 eyes were treated with intravitreal triamcinolone acetonide injection. Baseline central foveal thickness averaged 540 microns for the 16 enrolled eyes when measured by optical coherence tomography.

- For 14 eyes evaluated at 1-month, mean foveal thickness decreased from 533 microns to 242 microns. Two eyes did not complete the 1-month follow-up examination.
- 14 eyes evaluated at 3 months showed a reduction in mean foveal thickness from 528 microns to 224 microns. Two eyes did not complete the 3-month examination; these were different eyes than those that did not complete the 1-month examination.
- 8 eyes completing 6 months of follow-up showed a reduction in mean foveal thickness from 540 microns to 335 microns.
- Mean Snellen visual acuity improved by 2.4, 2.4, and 1.3 lines at the 1, 3, and 6-month follow-up intervals, respectively. No eyes lost vision at 1-month and all but 1 eye showed improvement ranging from 1 to 5 lines; 9 of 14 (64%) eyes showed improvement of 2 or more lines at this interval. No eyes lost vision from baseline at 3 months, and all but 1 eye showed improvement ranging from 1 to 5 lines; 9 of 14 (64%) eyes showed improvement of 2 or more lines at the 3-month interval. One eye lost a single line from baseline at 6 months and 1 eye remained stable; the other 6 eyes maintained improved visual acuity ranging from 1 to 3 Snellen lines. Four of 8 (50%) eyes maintained a visual improvement of 2 or more lines from baseline at the 6-month follow-up.

**Jonas et al**

An initial case report by Jonas and Sofker described a patient with non-proliferative diabetic retinopathy with a six month history of persistent, diffuse macular edema despite grid photocoagulation.[25] Following one intravitreal injection of 20mg/0.2cc of triamcinolone acetonide the visual acuity of this patient improved from 20/200 to 20/50 over a 5-month follow-up period. It was also noted that there was marked regression of macular edema on clinical examination.

Another report by Jonas et al described the results of intravitreal triamcinolone acetonide injection in 26 eyes with macular edema due to diabetic retinopathy.[41] All 26 eyes had visual acuity loss due to diabetic macular edema for at least 1 year and visual acuity was documented to be stable for at least 3 months. Grid laser photocoagulation had been performed in 9 of the 26 eyes prior to intravitreal injection. Twenty-five eyes were given one intravitreal injection of triamcinolone acetonide (25mg/.02cc) and one eye received 2 injections. The mean follow-up time was 6.6 months.

- Fluorescein angiography was performed on all patients before intravitreal injection. Twenty-one fluorescein angiograms were available following intravitreal injection. For the 21 patients where both the pre-injection and post-injection fluorescein angiogram was available, subjective evaluation showed decreased fluorescein leakage following intravitreal injection in all patients.
- Visual acuity was measured as best-corrected visual acuity and improved from a mean of 20/165 at baseline to a mean of 20/105 at the end of follow-up. In comparison, 16 patients followed in a "control group" that received grid laser photocoagulation showed no improvement in visual acuity.

**Massin et al**

Massin et al reported results obtained from injecting intravitreal triamcinolone acetonide (4mg/.1cc) into one eye of 15 patients with bilateral diffuse diabetic macular edema.[51] The patient's other eye served as a control for the study. All 30 eyes were unresponsive to 1 to 4 sessions of focal/grid laser photocoagulation, during which all focal leaks were treated. Results are provided for 12 patients with at least 24 weeks (3 months) of follow-up. The duration of diabetic macular edema, although difficult to exactly determine, ranged from 23 months to 72 months. Baseline central macular thickness measured on optical coherence tomography, averaged 510 microns for the 12 eyes injected with triamcinolone acetonide, and 474 microns for the 12 eyes in the control group. Baseline ETDRS visual acuity, averaged 47.8 and 51.9 letters in the injection and control groups respectively.

- 12 eyes injected with triamcinolone acetonide evaluated at 4 weeks demonstrated a decrease in macular thickness from 510 microns to 207 microns. This decrease was sustained through 12 weeks of follow-up. Seven eyes with a 24-week follow-up exam averaged 426 microns, reverting back towards the mean baseline thickness. The mean central macular thickness of the 12 eyes in the control group remained essentially constant throughout the 24 weeks. There was a significant difference between central macular thickness of injected and control eyes at 4 and 12 weeks (p-value < .05). This difference was not sustained at 24 weeks.

- At 12 weeks, 9 of the 12 injected eyes had normal (<206 microns) central macular thickness. Of the other three eyes, one showed an increase in macular thickness. No eyes in the control group had normal thickness and 7 eyes had an increase from baseline. At 24 weeks, 1 of the 7 injected eyes had normal central macular thickness and 4 eyes had an increase in thickness from baseline while no eyes in the control group had normal thickness and 3 eyes had an increase from baseline.

- Mean ETDRS best-corrected visual acuity scores improved in injected eyes from 47.8 letters at baseline to 53.4 letters at 4 weeks and to 52.7 letters at 12 weeks, an increase of 5.6 letters and 4.9 letters respectively. Control eyes averaged 51.9 letters at baseline compared with 52.5 letters at 4 weeks and 50.8 letters at 12 weeks, an increase of .6 letters at 4 weeks and a decrease of 1.1 letters at 12 weeks. The difference between the injection and control eyes were not statistically significant at any time point.

- At 12 weeks, best-corrected visual acuity had improved by at least 2 lines (10 letters) in 5 of the 12 eyes in the injection group and in none of the 12 control eyes.

**1.1.5.2 Adverse Effects (published series)**

**Martidis et al**

Elevated Intraocular Pressure

- 5 of 14 eyes that were evaluated at the 1-month follow-up had an intraocular pressure that exceeded 21 mmHg. The intraocular pressure in all 5 eyes was controlled successfully with one topical aqueous suppressant.

- Two of 14 eyes that were evaluated at the 3-month follow-up had an intraocular pressure that exceeded 21 mmHg. The intraocular pressure in both eyes was controlled successfully with one topical aqueous suppressant.

- One of 8 eyes that were evaluated at the 6-month follow-up had an intraocular pressure that exceeded 21 mmHg. The intraocular pressure in this eye was controlled successfully with one topical aqueous suppressant.
- The average intraocular pressure increased 45%, 20% and 13% from baseline at the 1, 3 and 6-month follow-up intervals respectively.

Cataract progression that did not require surgery was noted in one eye at the 6-month follow-up.

No complications such as retinal detachment, endophthalmitis, or vitreous hemorrhage were noted in this study.

**Jonas et al**

Elevated Intraocular Pressure

- Intraocular pressure exceeded 21 mmHg in 9 of the 26 eyes.
- The mean intraocular pressure increased from 16.9 mmHg at baseline to a maximal value of 21.3 mmHg during follow-up and decreased to 18.3 mmHg at the 7-month follow-up.
- The 9 eyes with an intraocular pressure elevation above 21 mmHg were treated with topical anti-glaucoma medication.
- No glaucomatous optic nerve damage was detected in any of these eyes and the intraocular pressure was normalized in all of these eyes.

No significant posterior subcapsular cataract or nuclear sclerosis was identified in any of the 18 phakic eyes.

No cases of post-operative infectious endophthalmitis occurred.

**Massin et al**

Elevated Intraocular Pressure

- Intraocular pressure exceeded 25 mmHg in 6 of 12 eyes, with a maximum of 32 mmHg. In all instances the pressure was controlled by topical medication with apraclonidine or dorzolamide.
- The mean intraocular pressure increased from a mean of 18.2 mmHg at baseline to 20.8 mmHg at 4 weeks and 20.5 mmHg at 12 weeks.

None of the 10 phakic eyes experienced cataract progression.

No complications related to the injection were detected during the study.

### 1.1.6 Clinical Studies (unpublished series)

**Martidis et al**

Martidis et al reported results using intravitreal triamcinolone acetonide injection (4mg/0.1cc) in 125 eyes with macular edema due to diabetic retinopathy (Presented at the combined Vitreous Society and Retina Society Meeting, San Francisco, CA on September 30, 2002). All 125 eyes had macular edema refractory to at least 2 sessions of laser photocoagulation.

- Mean baseline Snellen acuity was 20/160 and improved to 20/100 after a mean of 6.7 months of follow-up.
- 58% of eyes improved 2 or more Snellen lines at the end of follow-up.
- In eyes that had OCT performed, mean retinal thickness decreased 48% from a baseline of 484 microns to 251 microns at the end of follow-up.
- Intraocular pressure was >21 mmHg in 36% of eyes and >30 mmHg in 6% of eyes; one eye required trabeculectomy.
- Cataract progression was noted in 6% of eyes, but was seen only in eyes with more than 1 year of follow-up and represented 40% of this group; 3 eyes underwent cataract extraction at an average of 19 months post-injection.
- There was one eye that developed infectious endophthalmitis following injection.

**Pollack et al**

Pollack et al reported results using intravitreal triamcinolone acetonide injection (4mg/0.1cc) in 6 eyes with macular edema due to diabetic retinopathy (Presented at the combined Vitreous Society and Retina Society Meeting, San Francisco, CA on September 30, 2002). All 6 eyes had macular edema refractory to prior laser photocoagulation. Follow-up intervals ranged from 3-9 months.

- Macular edema was noted to resolve following a single injection in all 6 eyes.
- Visual acuity improved following a single injection in all 6 eyes.
- Fluorescein leakage in the macula significantly decreased following a single injection in all 6 eyes.
- Peak intraocular pressure of 25 mmHg to 34 mmHg occurred in 3 eyes.
- There was mild cataract progression in 3 of 3 phakic eyes.
- No cases of infectious endophthalmitis or retinal detachment occurred.

### 1.1.7 Studies Evaluating Corticosteroid Preparations Other than Triamcinolone

**Efficacy**

**Control Delivery Systems (Bausch and Lomb)**

Control Delivery Systems (Bausch and Lomb) is developing a non-biodegradable, implantable, extended release product that delivers the corticosteroid fluocinolone acetonide directly to the posterior segment for a period of 3 years. A multi-center, randomized, masked trial is currently being conducted to evaluate this technology for the treatment of diabetic macular edema refractory to prior laser photocoagulation. Eligible visual acuity ranged from 20/50 to 20/400, inclusive. This trial enrolled 80 patients with diabetic macular edema. Patients were randomly assigned to one of three treatment arms: 0.5mg implant (N=41), 2mg implant (N=11), or standard of care treatment consisting of either repeat laser photocoagulation or observation (N=28). The 6-month data presented below were presented at the combined Vitreous Society and Retina Society Meeting, San Francisco, CA on September 30, 2002. The 12-month data presented below were presented at the Association for Research in Vision and Ophthalmology Meeting, Ft. Lauderdale FL on May 8, 2003.

- At the 6-month follow-up, the proportion of eyes with maintained or improved visual acuity was greater in eyes that received the 0.5mg implant than those assigned to standard of care treatment ($P<0.01$). This result was not statistically significant at the 12-month follow-up.

- At the 6-month follow-up, the proportion of eyes with a 2 or more step decrease in retinal thickening at the center of the fovea was greater in eyes that received the 0.5mg implant than those assigned to standard of care treatment (P=0.03). This result remained statistically significant at the 12-month follow-up (P=0.003).

- At the 6-month follow-up, 12.2% of patients in the 0.5mg implant group had an intraocular pressure elevation to 30 mmHg or more. All patients were managed with topical anti-glaucoma medication. No eye in the standard of care group had such an elevation in intraocular pressure. At the 12-month follow-up, 19.5% of patients in the 0.5mg implant group had an intraocular pressure elevation that was considered a serious adverse event. Three patients in the 0.5mg implant group required trabeculectomy surgery. No eye in the standard of care group had such an elevation in intraocular pressure.

**Oculex**

Oculex is developing a biodegradable, implantable, extended release product (Posurdex) that delivers the corticosteroid dexamethasone directly to the posterior segment for a period of 35 days. A phase 2 clinical trial was completed evaluating 2 dosages of Posurdex, 350 micrograms and 700 micrograms. Patients with macular edema due to diabetic retinopathy, retinal vascular occlusive disease, Irvine-Gass syndrome, or uveitis were included. Eligible visual acuity was 20/40-20/200. Patients were randomized to one of three treatment arms: 350 microgram implant, 700 microgram implant, or observation. 306 patients were enrolled, 172 with diabetic macular edema, 103 with vein occlusion, 27 with Irvine-Gass syndrome, and 14 with uveitic macular edema.

- Patients receiving the 700 microgram implant had a statistically significant improvement in visual acuity of 2 or more lines on the ETDRS chart when compared with patients who did not receive the implant (P=0.02).

- Secondary outcomes such as retinal thickness and fluorescein leakage also showed statistically significant decreases in patients that received the 700 microgram implant when compared with patients who did not receive the implant (P=0.001).

- Patients receiving the 350 microgram implant also demonstrated statistically significant decreases in retinal thickness and fluorescein leakage, with a trend towards improvement in visual acuity, indicating a dose response to the treatment.

- An intraocular pressure elevation to 25 mmHg or more was noted at some point in the study in 32 eyes, all were readily controlled with topical anti-glaucoma medication.

- There was no difference in cataract progression between the study groups.

### 1.1.8 Other Studies Using Intravitreal Triamcinolone for Indications Other Than Diabetic Macular Edema

Clinical studies evaluating intravitreal triamcinolone acetonide injection for indications other than diabetic macular edema are pertinent because it is believed the injection-related complications, such as retinal detachment and endophthalmitis, and the steroid-related complications, such as cataract and glaucoma, are likely to be similar across disease groups. These studies are summarized in Table 2.

Penfold and Challa studied 30 eyes with exudative macular degeneration.[35, 36] No adverse events such as retinal detachment, vitreous hemorrhage or endophthalmitis were noted. However, 3 of 4 eyes that received a second injection of triamcinolone acetonide experienced rapid progression of cataract within 2 months of re-injection. Two of these 4 eyes also experienced steroid-induced

glaucoma with intraocular pressure elevation to 37 mmHg. Both eyes had argon laser trabeculoplasty and were treated with topical aqueous suppressants. One of these 2 eyes required trabeculectomy surgery to control intraocular pressure.

In another series, Danis et al injected 16 eyes with exudative macular degeneration.[37] No adverse events such as retinal detachment, vitreous hemorrhage or endophthalmitis were noted. Four of seven phakic patients developed progressive lens opacities that did not require cataract surgery over the 6-month follow-up. Four patients developed transient intraocular pressure elevation that required one to two topical aqueous suppressants to lower the intraocular pressure to less than 25 mmHg; all patients eventually had topical therapy discontinued. No patient had intraocular pressure over 32 mmHg at any point in follow-up.

The other studies listed in Table 2 all demonstrate a similar adverse event profile.[24, 34, 52, 53] A summary of the data from the 7 studies listed shows that injection-related adverse events such as endophthalmitis, pseudoendophthalmitis, retinal detachment, and vitreous hemorrhage appear uncommon, at least in the published literature. Adverse events specifically attributed to the corticosteroid (cataract and glaucoma) are more common but appear to be manageable. For example, of the 221 patients in the 7 studies discussed, 33 patients (15%) were noted to have some elevation of intraocular pressure; all patients were managed successfully with topical aqueous suppressants, except 1 patient who required trabeculectomy. Nine patients (4%) required cataract surgery and 24 patients (12%) were noted to have progressive lens opacity.

**Table 2: Safety of Intravitreal Steroids - clinical studies (published studies)**

| | # eyes | Disease | Dose (mg) | IOP rise | Cataract (surgery) | Lens Opacity | R.D. | Vit Heme | End-ophth | Pseudo-endophth |
|---|---|---|---|---|---|---|---|---|---|---|
| Wingate[52] | 113 | AMD | 4 | 12 | 0(?) | 0(?) | 0(?) | 0(?) | 0(?) | 0(?) |
| Penfold[35] | 30 | AMD | 4 | 3 | 9 | 1 | 0 | 0 | 0 | 0 |
| Danis[37] | 16 | AMD | 4 | 4 | 0 | 4/7 phakic | 0 | 0 | 0 | 0 |
| Jonas[34] | 16 | PVR | 10-20 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Martidis[24] | 16 | DME | 4 | 5 | 0 | 1 | 0 | 0 | 0 | 0 |
| Jonas[53] | 4 | NVG | 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Jonas[41] | 26 | DME | 25 | 9 | 0 | 18/18 phakic (P=.16) | 0 | 0 | 0 | 0 |
| 7 Studies (pooled) | 221 | | | 33 (15%) | 9 (4%) | 24 (12%) | 0 | 0 | 0 | 1 |

? = was not evaluated in this study

## 1.2 Summary of Rationale for a Randomized Trial

1. Macular edema is a common cause of visual loss in patients with diabetes.
2. Although laser photocoagulation has been demonstrated to be beneficial in reducing further vision loss, vision that has already been decreased by macular edema usually does not improve. Identification of a treatment that could improve vision is desirable and of public health importance.
3. The results of treating DME with intravitreal corticosteroids appear promising. However, a controlled study has not been performed and the reported promising results are primarily for short-term follow-up.
4. Currently, Kenalog is being used for intravitreal injection because a preservative-free corticosteroid preparation for intraocular use is not available. Because of the risk of noninfectious endophthalmitis from the Kenalog vehicle, development of a corticosteroid for intraocular use would be highly desirable.
5. Corticosteroids have known ocular toxicity, in particular glaucoma and cataract. Because a controlled study has not been performed and reported follow-up on treated cases has been principally short-term, the incidence of these complications is not known. This information is critical for establishing a risk-benefit ratio for intravitreal corticosteroid injections.
6. It is estimated that several thousand patients have received intravitreal corticosteroids for DME despite the lack of evidence of long-term efficacy and lack of information on whether the benefits outweigh the risks. Therefore, a randomized trial is needed to provide definitive data on whether the benefits of this treatment outweigh the risks.

7. After the risks and benefits of intravitreal corticosteroids are known from a well-conducted study, it is possible that laser photocoagulation will prove to be the preferred treatment. Therefore, randomization to either laser or intravitreal corticosteroids is not only scientifically important but also unequivocally ethical. Because of concerns about the potential risks, patients in the trial will receive intravitreal corticosteroids in only one eye.

### 1.3 Rationale for the Steroid Doses to Be Evaluated in the Trial

The optimal dose of corticosteroid to maximize efficacy with minimum side effects is not known. A 4mg dose of Kenalog is principally being used in clinical practice. However, this dose has been used based on feasibility rather than scientific principles.

There is also experience using doses of 1mg and 2mg. These doses anecdotally have been reported to reduce the macular edema. There is a rationale for using a dose lower than 4mg.[54, 55] Glucocorticoids bind to glucocorticoid receptors in the cell cytoplasm, and the steroid-receptor complex moves to the nucleus where it regulates gene expression. The steroid-receptor binding occurs with high affinity (low dissociation constant (Kd) which is on the order of 5 to 9 nanomolar). Complete saturation of all the receptors occurs about 20-fold higher levels, i.e., about 100-200 nanomolar. A 4mg dose of triamcinolone yields a final concentration of 7.5 millimolar, or nearly 10,000-fold more than the saturation dose. Thus, the effect of a 1mg dose may be equivalent to that of a 4mg dose, because compared to the 10,000-fold saturation, a 4-fold difference in dose is inconsequential. It is also possible that higher doses of corticosteroid could be less effective than lower doses due to down-regulation of the receptor. The steroid implant studies provide additional justification for evaluating a lower dose, a 0.5mg device which delivers only 0.5 micrograms per day has been observed to have a rapid effect in reducing macular edema (P. Andrew Pearson, personal communication).

There has been limited experience using doses greater than 4mg. Jonas' case series described earlier reported results using a 25mg dose. However, others have not been able to replicate this dose using the preparation procedure described by Jonas (Frederick Ferris, personal communication).

In the trial, 4mg and 1mg doses will be evaluated. The former will be used because it is the dose that is currently most commonly used in clinical practice and the latter because there is reasonable evidence for efficacy and the potential for lower risk. Although there is good reason to believe that a 1mg dose will reduce the macular edema, it is possible that the retreatment rate will be higher with this dose compared with 4mg since the latter will remain active in the eye for a longer duration than the former. Insufficient data are available to warrant evaluating a dose higher than 4mg at this time.

### 1.4 Study Objectives

Primary Objectives

- To determine whether intravitreal triamcinolone acetonide injections at doses of 1mg or 4mg produce greater benefit, with an acceptable safety profile, than macular laser photocoagulation in the treatment of diabetic macular edema.
- To compare the efficacy and safety of the 1mg and 4mg triamcinolone acetonide doses.

## 1.5 Study Design and Synopsis of Protocol

### A. Study Design

- Randomized, multi-center clinical trial.

### B. Major Eligibility Criteria

- Age >=18 years.
- Study eye with best corrected E-ETDRS acuity >= 24 letters (20/320 or better) and <=73 letters (20/40 or worse).
- Study eye with center-involved DME present on clinical exam and on OCT.
- Fellow eye either eligible or has acuity >=19 letters (20/400 or better) and has not been previously treated with intravitreal corticosteroids.

### C. Treatment Groups

Randomization to one of three treatment groups:

1) Standard of care group: conventional treatment consisting of focal/grid photocoagulation.
2) Intravitreal injection of 1mg of triamcinolone acetonide.
3) Intravitreal injection of 4mg of triamcinolone acetonide.

*Patients may have one or two study eyes. Patients with two study eyes will receive photocoagulation in one eye and intravitreal triamcinolone acetonide, 1mg or 4mg dose, in the other eye. Patients and investigators will be masked to the triamcinolone acetonide dose (1mg or 4mg).*

*Conditions whereby eyes randomized to laser photocoagulation may receive intravitreal triamcinolone acetonide and conditions whereby eyes randomized to intravitreal triamcinolone acetonide may receive laser photocoagulation are detailed in section 5.5.*

**D. Duration of Follow-Up:** Three years.

### E. Main Efficacy Outcomes

Primary: Visual acuity (measured with E-ETDRS)

Secondary: Retinal thickening (measured on OCT)

### F. Main Safety Outcomes

(1) Intraocular pressure elevation/glaucoma, (2) cataract, (3) endophthalmitis (bacterial or inflammatory), (4) retinal detachment.

### G. Timing of Outcome Assessments

Primary outcome at 3 years (preliminary outcome assessment at 1 year).

**H. Sample Size:** 795 patients.

## I. Schedule of Study Visits and Examination Procedures

| | Study Month | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **0** | **4** | **8*** | **12** | **16*** | **20*** | **24** | **28*** | **32*** | **36** |
| E-ETDRS visual acuity[a] | x | x | x | x | x | x | x | x | x | x |
| Fundus photos | 7F | 3F | | 7F | | | 7F | | | 7F |
| OCT [b] | x | x | x | x | x | x | x | x | x | x |
| IOP | x | x | x | x | x | x | x | x | x | x |
| Eye Exam[c] | x | x | x | x | x | x | x | x | x | x |
| Blood pressure | x | | | x | | | x | | | x |
| HbA1c[d] | x | | | x | | | x | | | x |
| Fluor. Angio[e] | x | | | | | | | | | |
| PK Blood Draws[f] | x | x | | | | | | | | |

Testing is on both eyes at each visit unless otherwise specified below.

a=includes protocol refraction at 0, 4, 12, 24, and 36 months. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.[56]

b=performed on both eyes at 0 (performed twice), 4, 12, 24, and 36 months and on the study eye only at other visits

c=includes lens assessment using standard photos at 0, 4, 12, 24, and 36 months (selected sites will obtain lens photos with Neitz and slit lamp cameras)

d=does not need to be repeated if HbA1c and lab normal values are available from within the prior 3 months (at baseline, can be performed within 3 weeks after randomization)

e=does not need to be performed if not part of usual care.

f= only at selected sites for patients randomized to either of the triamcinolone acetonide treatment groups.

*visit window may be extended if necessary for visit to occur no sooner than 3.5 months from the last treatment

In the intravitreal triamcinolone acetonide groups, standard of care post-treatment visits occur 4 days and 4 weeks after each intravitreal injection. Data collected at these visits will be analyzed under the assumption that none of the recorded adverse events would have occurred in the absence of the treatment.

Approximately 40 patients from the 1mg and 4mg intravitreal triamcinolone acetonide treatment groups (at selected sites) will have blood drawn at specified visits for measuring plasma triamcinolone acetonide concentrations.

In the laser photocoagulation group, a treatment session may be given in multiple sittings, necessitating additional visits.

## 1.6 General Considerations

The study is being conducted in compliance with the policies described in the DRCRnet Policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

The Investigator Brochure provides details about the properties of the study drug and its formulation.

The DRCRnet Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, Photography Testing Procedures Manual, and Study Procedures Manual) provide details of the examination procedures and intravitreal injection procedure.

Data will be directly collected in electronic case report forms, which will be considered the source data.

There is no restriction on the number of patients to be enrolled by a site.

# CHAPTER 2.
# SUBJECT ELIGIBILITY AND ENROLLMENT

## 2.1 Identifying Eligible Subjects and Obtaining Informed Consent

A minimum of 795 patients are expected to be enrolled with a goal to enroll an appropriate representation of minorities. Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For subjects who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the patient by a study investigator and clinic coordinator. The patient will be given the Informed Consent Form to read. Patients will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study.

Consent may be given in two stages (if approved by the IRB). The initial stage will provide consent to complete any of the screening procedures needed to assess eligibility that have not already been performed as part of a usual-care exam. The second stage will be obtained prior to randomization and will be for participation in the study. A single consent form will have two signature/date lines for the patient: one for the patient to give consent for the completion of the screening procedures and one for the patient to give consent for the randomized trial. Patients will be provided with a copy of the signed Informed Consent Form.

Once a patient is randomized, that patient will be counted regardless of whether the assigned treatment is received or not. Thus, the investigator must not proceed to randomize a patient until he/she is convinced that the patient will accept assignment to any one of the three treatment groups.

## 2.2 Patient Eligibility Criteria

### 2.2.1 Subject-level Criteria

Inclusion

***To be eligible, the following inclusion criteria (1-6) must be met:***

1. Age >= 18 years
   - *Patients <18 years old are not being included because DME is so rare in this age group that the diagnosis of DME may be questionable.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes*
     - *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes*
     - *Documented diabetes by ADA and/or WHO criteria*
3. At least one eye meets the study eye criteria listed in section 2.2.2.
4. If only one eye eligible, fellow eye meets criteria in section 2.2.3.
5. Able and willing to provide informed consent.

6. Patient understands that (1) if both eyes are eligible at the time of randomization, one eye will receive intravitreal triamcinolone acetonide and one eye will receive laser, and (2) if only one eye is eligible at the time of randomization and the fellow eye develops DME later, then the fellow eye will not receive intravitreal triamcinolone acetonide if the study eye received intravitreal triamcinolone acetonide *(however, if the study eye was assigned to the laser group, then the fellow eye may be treated with the 4mg dose of the study intravitreal triamcinolone acetonide formulation, provided the eye assigned to laser has not received an intravitreal injection; such an eye will not be a 'study eye' but since it is receiving study drug, it will be followed for adverse effects).*

Exclusion

***A patient is not eligible if any of the following exclusion criteria (7-13) are present:***

7. History of chronic renal failure requiring dialysis or kidney transplant.
8. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure and glycemic control).
   - *Patients in poor glycemic control who, within the last 4 months, initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next 4 months should not be enrolled.*
9. Participation in an investigational trial within 30 days of study entry that involved treatment with any drug that has not received regulatory approval at the time of study entry.
10. Known allergy to any corticosteroid or any component of the delivery vehicle.
11. History of systemic (e.g., oral, IV, IM, epidural, bursal) corticosteroids within 4 months prior to randomization or topical, rectal, or inhaled corticosteroids in current use more than 2 times per week.
12. Patient is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the 3 years of the study.
13. Blood pressure > 180/110 (systolic above 180 **OR** diastolic above 110).
    - *If blood pressure is brought below 180/110 by anti-hypertensive treatment, patient can become eligible.*

### 2.2.2 Study Eye Criteria

The patient must have at least one eye meeting all of the inclusion criteria (a-d) and none of the exclusion criteria (e-x) listed below.

A patient may have two study eyes only if both are eligible at the time of randomization.

The eligibility criteria for a study eye are as follows:

Inclusion

a. Best corrected E-ETDRS visual acuity score of >= 24 letters (i.e., 20/320 or better) and <= 73 letters (i.e., 20/40 or worse).
b. Definite retinal thickening due to diabetic macular edema based on clinical exam involving the center of the macula.
c. Mean retinal thickness on two OCT measurements >=250 microns in the central subfield.

d. Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

Exclusion

e. Macular edema is considered to be due to a cause other than diabetic macular edema.
   - *An eye should not be considered eligible: (1) if the macular edema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggests that vitreoretinal interface disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular edema.*

f. An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition).

g. An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.).

h. Substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal).

i. History of prior treatment with intravitreal corticosteroids.

j. History of peribulbar steroid injection within 6 months prior to randomization.

k. History of focal/grid macular photocoagulation within 15 weeks (3.5 months) prior to randomization.
   - *Note: Patients are not required to have had prior macular photocoagulation to be enrolled.*
   - *Note: If prior macular photocoagulation has been performed, the investigator should believe that the patient may possibly benefit from additional photocoagulation.*

l. History of panretinal scatter photocoagulation (PRP) within 4 months prior to randomization.

m. Anticipated need for PRP in the 4 months following randomization.

n. History of prior pars plana vitrectomy.

o. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 6 months or anticipated within the next 6 months following randomization.

p. History of YAG capsulotomy performed within 2 months prior to randomization.

q. Intraocular pressure >= 25 mmHg.

r. History of open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma; note: angle-closure glaucoma is not an exclusion).
   - *A history of ocular hypertension is not an exclusion as long as (1) intraocular pressure is <25 mm Hg, (2) the patient is using no more than one topical glaucoma medication, (3) the most recent visual field, performed within the last 12 months, is normal (if abnormalities are present on the visual field they must be attributable to the patient's diabetic retinopathy), and (4) the optic disc does not appear glaucomatous.*

- *Note: if the intraocular pressure is 22 to <25 mm Hg, then the above criteria for ocular hypertension eligibility must be met.*

s. History of steroid-induced intraocular pressure elevation that required IOP-lowering treatment.

t. History of prior herpetic ocular infection.

u. Exam evidence of ocular toxoplasmosis.

v. Aphakia.

w. Exam evidence of pseudoexfoliation.

x. Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis.

**2.2.3 Fellow Eye Criteria**

In patients with only one eye meeting criteria to be a study eye at the time of randomization, the fellow eye must meet the following criteria:

a. Best corrected E-ETDRS visual acuity score >= 19 letters (i.e., 20/400 or better).

b. No prior treatment with intravitreal corticosteroids.

c. Intraocular pressure < 25 mmHg.

d. No history of open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma; note: angle-closure glaucoma is not an exclusion).
   - *A history of ocular hypertension is not an exclusion as long as (1) intraocular pressure is <25 mmHg, (2) the patient is using no more than one topical glaucoma medication, (3) the most recent visual field, performed within the last 12 months, is normal (if abnormalities are present on the visual field they must be attributable to the patient's diabetic retinopathy), and (4) the optic disc does not appear glaucomatous.*
   - *Note: if the intraocular pressure is 22 to <25 mmHg, then the above criteria for ocular hypertension eligibility must be met.*

e. No history of steroid-induced intraocular pressure elevation that required IOP-lowering treatment.

f. No exam evidence of pseudoexfoliation.

## 2.3. Screening Evaluation and Baseline Testing

### 2.3.1 Historical Information

A history will be elicited from the patient and extracted from available medical records. Data to be collected will include: age, gender, ethnicity and race, diabetes history and current management, other medical conditions, medications being used, and ocular diseases, surgeries, and treatment.

### 2.3.2 Testing Procedures

The following procedures are needed to assess eligibility and/or to serve as a baseline measure for the study.

If a procedure has been performed (using the study technique and by study certified personnel) as part of usual care, it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.

The testing procedures are detailed in the DRCRnet Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, Photography Testing Procedures Manual, and Study Procedures Manual). Visual acuity testing, ocular exam, fundus photography, OCT, and lens assessment will be performed by certified personnel.

In some cases, assessment of eligibility and the baseline treatment (laser or intravitreal triamcinolone acetonide injection, which must be given on day of randomization) will require at least two visits. For this reason, maximum time windows from the completion of each procedure to the day of randomization have been established.

Testing will be performed on each eye.

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye *(done within 8 days prior to randomization).*
   - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[56]
2. OCT *(done within 21 days prior to randomization).*
   - *Measurements will be made twice.*
3. Ocular examination on study eye, including slit lamp and dilated fundus examination *(done within 21 days prior to randomization).*
4. Lens assessment *(done within 21 days prior to randomization).*
   - *Standard photographs will be used for the assessment of nuclear sclerosis, posterior subcapsular changes, and cortical changes.*
   - *Note: the Reading Center will assess posterior subcapsular and cortical lens changes from reflex photographs.*
   - *Selected sites may obtain lens photos using a Neitz camera and a slit lamp camera.*
5. Measurement of intraocular pressure (using Goldmann tonometer) *(done within 21 days prior to randomization).*
6. ETDRS protocol 7-standard field stereoscopic fundus photography (fields 1M, 2, 3M, 4, 5, 6, 7, reflex) *(done within 21 days prior to randomization).*
7. Measurement of blood pressure *(done within 21 days prior to randomization).*
8. HbA1c blood test.
   - *Does not need to be repeated if available in the prior 3 months. If not available at the time of randomization, the patient may be enrolled but the test must be obtained within 3 weeks after randomization.*

A fluorescein angiogram is not required. However, if a fluorescein angiogram is performed as part of usual care, the angiogram will be submitted to the Reading Center. Results of the angiogram are not required prior to initiating laser treatment or intravitreal injection.

## 2.4 Enrollment/Randomization of Eligible Patients

The fundus photographs and OCT will be sent to the Fundus Photograph Reading Center for grading, but patient eligibility is determined by the site (i.e., patients deemed eligible by the investigator will be randomized without need for Reading Center confirmation).

1. Prior to randomization, the patient's understanding of the trial, willingness to accept the assigned treatment group, and commitment to the follow-up schedule should be reconfirmed.

2. Treatment (photocoagulation or intravitreal triamcinolone acetonide injection) must be given on the day of randomization; therefore, a patient should not be randomized until this is possible.
   - For patients with two study eyes, the intravitreal triamcinolone acetonide injection will be performed on the day of randomization and the laser will be performed either on the same day or within 7 days of randomization.

3. Randomization is completed on the DRCRnet website.
   - Patients with one study eye will be randomly assigned (stratified by visual acuity and prior laser) with equal probability to one of the three treatment groups:
     1) Laser photocoagulation (see chapter 3).
     2) 1mg intravitreal triamcinolone acetonide injection (see chapter 4).
     3) 4mg intravitreal triamcinolone acetonide injection (see chapter 4).
   - For patients with two study eyes (both eyes eligible at the time of randomization), the right eye (stratified by visual acuity and prior laser) will be randomly assigned with equal probabilities to one of the three treatment groups listed above. The left eye will be assigned to the alternative treatment (laser or triamcinolone). If the left eye is assigned to triamcinolone, then the dose (1mg or 4 mg) will be randomly assigned to the left eye with equal probability (stratified by visual acuity and prior laser).

# CHAPTER 3.
# MACULAR LASER PHOTOCOAGULATION

## 3.1 Introduction

In patients with a single study eye assigned to laser photocoagulation, the laser photocoagulation will be given on the day of randomization. In patients with two study eyes, the study eye assigned to the laser group will be treated with photocoagulation on the day of randomization or within 7 days of randomization (the other eye will be treated with an intravitreal injection on the day of randomization).

The laser treatment 'session' may be completed fully at the initial 'sitting', or it may be divided into multiple sittings at the investigator's discretion, as long as the entire treatment session is completed within 6 weeks.

The timing of, and criteria for, retreatment with laser photocoagulation are detailed in section 5.4.

## 3.2 Photocoagulation Technique

The photocoagulation treatment technique, as described below, is a modification of the ETDRS technique and is the treatment approach that is commonly used in clinical practice. This technique is followed for both the initial treatment and for retreatment.

A fluorescein angiogram may be used to guide retreatment at the investigator's discretion; if performed, it will not be sent to the Reading Center (however, fluorescein angiograms performed at baseline will be sent to the Reading Center). Post-treatment photographs (field 2 stereo) may be requested on selected patients by the Reading Center.

| Burn Characteristic | Focal / Grid Photocoagulation (modified-ETDRS technique) |
|---|---|
| **Area Considered for Treatment** | 500 to 3000 microns from the center of macula<br>No burns are placed within 500 microns of optic disk |
| **Wavelength:** | Green to yellow wavelengths |
| **Burn Size** | 50 microns |
| **Burn Duration** | 0.05 to 0.1 sec |
| **Grid Treatment** | If fluorescein angiography is performed: apply to all areas of diffuse leakage or nonperfusion within the area outlined above as well as to all areas with retinal thickening within the area outlined above<br><br>If fluorescein angiography is not performed: apply to all areas with retinal thickening within the area outlined above |
| **Burn Intensity** | Barely visible (light grey) |
| **Burn Separation** | 2 visible burn widths apart |
| **Focally Treat Leaking MA** | All leaking microaneurysms are focally treated, but only in areas of retinal thickening located within treatment area outlined above |
| **Change MA Color** | Not required, but at least a mild burn should be evident beneath all MAs |

MA = microaneurysm

*Note:*

- *The investigator may choose any laser wavelength for photocoagulation within the green to yellow spectrum. The wavelength used will be recorded and any retreatment should use the same wavelength.*
- *Lenses used for the laser treatment cannot increase or reduce the burn size by more than 10%.*

# CHAPTER 4.
# INTRAVITREAL TRIAMCINOLONE INJECTION

## 4.1 Introduction

Study eyes assigned to an intravitreal triamcinolone injection will receive a dose of either 1mg or 4mg. The initial intravitreal triamcinolone injection will be given on the day of randomization.

The timing of, and criteria for, retreatment with intravitreal triamcinolone injection are detailed in section 5.4.

## 4.2 Triamcinolone Acetonide Preparation

The study drug, triamcinolone acetonide, has been manufactured as a sterile intravitreal injectable by Allergan. The physical, chemical, and pharmaceutical properties and formulation of the study triamcinolone acetonide preparation are provided in the Clinical Investigator's Brochure.

## 4.3 Treatment Technique

The injection is preceded by multiple instillations of a topical antibiotic followed by a povidone iodine prep. The injection will be performed using sterile technique. After the injection, topical antibiotics will be prescribed for three days. The same technique is followed for both the initial treatment and for retreatment. The full injection procedure is described in the DRCRnet Study Procedures Manual.

# CHAPTER 5.
# FOLLOW-UP VISITS AND ADDITIONAL TREATMENTS

## 5.1 Visit Schedule

Follow-up visits occur in each group every 4 months.

- The visits at 4, 12, 24, and 36-months are designated as outcome assessment visits. At these visits, certain additional testing is performed that is not performed at other visits.
- Visit windows are $\pm$ 2 weeks during year 1 and $\pm$ 8 weeks during years 2 and 3. For the visits at 8, 16, 20, 28, and 32-months, the end of the visit window may be extended if necessary so that the visit occurs no sooner than 3.5 months since the last treatment.

Additional visits may occur as required for usual care of the patient.

- In the intravitreal triamcinolone injection groups, standard of care post-treatment visits will be performed at 4 days and 4 weeks after each intravitreal injection.
- In the laser photocoagulation group, a treatment session may be given in multiple sittings necessitating additional visits.
- A patient's ocular condition may require additional visits.

## 5.2 Testing Procedures at 4-month Interval Protocol Visits

The following procedures will be performed at each visit and on both eyes unless otherwise specified.

All of the testing procedures do not need to be performed on the same day, provided that they are completed within the time window of a visit and prior to initiating any retreatment. A grid in section 1.5 summarizes the testing performed at each visit.

1. E- ETDRS visual acuity testing.
   - A protocol refraction is required at 4, 12, 24, and 36-months. At other visits, the need for a refraction is determined by the investigator based on usual care considerations. A refraction generally should be performed when there is an unexplained decrease in visual acuity of 15 or more letters.
2. Measurement of intraocular pressure (using Goldmann tonometer).
3. Slit lamp and dilated fundus examination.
4. Lens assessment
   - Standard photographs will be used for the assessment of nuclear sclerosis, posterior subcapsular changes, and cortical changes at the 4, 12, 24, and 36-month visits.
   - The Reading Center will assess posterior subcapsular and cortical lens changes from the reflex photographs that accompany the fundus photographs at the 4, 12, 24, and 36-month visits.
   - Selected sites may obtain lens photos using a Neitz camera and a slit lamp camera.
5. ETDRS protocol stereoscopic fundus photography.
   - ETDRS 7-fields (1M, 2, 3M, 4, 5, 6, 7, reflex) at 12, 24, and 36-month visits and 3-fields (1M, 2, 3M, reflex) at the 4-month visit.

6. OCT
   - Performed on both eyes at the 4, 12, 24, and 36-month visits and on the study eye only at other visits (two measurements may be made to assess reproducibility).
   - Should be performed using the same OCT machine version used at baseline (e.g., OCT1, OCT2, or OCT3 used throughout the study for a particular patient).
7. Measurement of blood pressure.
   - Performed at 12, 24, and 36-month visits only
8. HbA1c.
   - Performed at 12, 24, and 36-month visits only
   - If an HbA1c test result is available from the prior 3 months, it does not need to be repeated at these visits.

**5.3 Testing Procedures at Other Visits**

At the post-intravitreal injection visits, visual acuity will be measured, intraocular pressure will be measured, and slit lamp and dilated fundus exams will be performed on the treated eye.

At unscheduled visits, the procedures performed will be determined by the investigator.

**5.4 Retreatment Assessment**

At each 4-month interval visit, the investigator will assess whether persistent or recurrent DME is present that warrants retreatment with the randomization assigned treatment.

Retreatment, when indicated, will be performed within four weeks after the follow-up visit. Retreatment should not be performed sooner than 3.5 months from the time of the last treatment.

If retreatment is deferred because the patient has responded well to prior treatment (see section 5.4.1), then the patient can either be scheduled to be seen in 4 months or can be seen sooner at investigator's discretion.

**5.4.1 Retreatment Criteria**

In general, the patient will be retreated with the randomization-assigned treatment unless there are specific reasons not to retreat, in which case the investigator may decide to postpone treatment, although postponing treatment is not required. The reasons for not retreating include:

1. Treatment has been successful and may not need to be repeated if one of the following is present:
   a. The investigator considers the center of the macula nearly flat *(Note: for the purposes of this study, as a guideline, the center of the macula should <u>not</u> be considered flat if the OCT central subfield is >225 microns)*.
   b. Visual acuity score is 79 or more letters (20/25 or better).
   c. In the opinion of the investigator, there has been substantial improvement in macular edema from the last treatment session (e.g., >= 50% decrease in retinal <u>thickening</u> [thickening is not retinal thickness; it is the difference between normal retinal thickness and observed retinal thickness] in the central subfield) <u>AND</u> further spontaneous improvement (without additional treatment) in macular edema might be expected.

2. Additional treatment is contraindicated because either the patient had a significant adverse effect from prior treatment or maximum treatment has already been received.

   Examples include the following:

   - The patient had an intraocular pressure elevation after a previous treatment that required treatment. (*Note: Investigator may choose to retreat a patient who developed intraocular pressure elevation that is controlled with treatment as long as IOP currently is <=35 mmHg. If the IOP is > 35 mmHg then the IOP must be lowered before retreatment is given).*
   - In the investigator's judgment, maximum safe laser photocoagulation has been performed and therefore additional laser photocoagulation is contraindicated

3. Additional treatment "apparently futile":

   Treatment will be defined as "apparently futile" if 8 or more months transpire, during which there have been 2 procedures (either laser photocoagulation session or intravitreal triamcinolone injection, according to the randomization assigned treatment), and during which there is no evidence of at least borderline improvement.

   An eye is considered to have at least "borderline improvement" if it meets either of the following criteria compared with findings at the beginning of the 8 or more months period:

   a. An increase in visual acuity score of 5 or more letters.

   OR

   b. A decrease in calculated retinal thickening (measured thickness minus 175 microns in the OCT central subfield of the six-radial scan map) that is at least 50 microns and represents at least a 20% reduction in calculated retinal thickening compared with the findings at the beginning of the 8 or more month period indicated above.

   If the eye meets the criteria for additional treatment being "apparently futile" (i.e., does not meet criteria for having at least "borderline improvement"), the investigator may elect to discontinue further treatment at this visit. However, the investigator is not obligated to discontinue treatment at this visit and may continue treatment (either laser photocoagulation or intravitreal triamcinolone injection, according to the randomization assigned treatment) if desired.

   *Example:*
   *An eye improved in visual acuity from 20/80 to 20/40 and in OCT from 400 to 300 microns during the first year of follow-up (i.e., at the 12-month follow-up the visual acuity was 20/40 and the OCT measured 300 microns) and had intravitreal injections at baseline, 6, 12, and 16 months. Between 12 and 20 months the eye never had a visual acuity measured at better than 20/40 and the smallest OCT thickness measured was 290 (less than 50 microns reduction from 300 microns measured at 1-year). Because there is no evidence of at least "borderline improvement" during these last 8 months, the treating ophthalmologist may wish to discontinue treatment at this visit. However, continued treatment is not forbidden. If treatment is discontinued, the investigator may choose to reinstate treatment at a subsequent visit (such as, if the investigator believes that vision and/or retinal thickening has worsened).*

*If the OCT thickness at the beginning of the ≥8-month period had been 500µm, a reduction of at least 65µm would have been required to meet the at least "borderline improvement" definition (beginning calculated retinal thickening 500-175 = 325; 20% reduction = 65µm).*

Note: This example is for a patient assigned to receive intravitreal triamcinolone injection. However, this example is also applicable for patients assigned to receive laser photocoagulation.

**5.5 Alternative Treatment for the Study Eye**

Although it is preferable that study eyes assigned to the laser photocoagulation group not be treated with intravitreal triamcinolone acetonide and vice versa, it is recognized that there may be situations where the investigator strongly believes that the alternative treatment should be provided.

An eye may be treated with the alternative treatment when it has experienced:

1. A 15-letter decrease from baseline in best-corrected visual acuity that is present at two consecutive 4-month interval visits.

AND

2. The decrease in visual acuity is due to persistent or recurrent macular edema (i.e., not due to cataract or other abnormality) that is documented on OCT. *(Note: for the purposes of this study, as a guideline, the center of the macula should <u>not</u> be considered flat if the OCT central subfield is >225 microns)*.

When the above criteria are met, an eye assigned to the laser photocoagulation group may receive (but is not required to receive) intravitreal triamcinolone (4mg dose, study formulation) and an eye assigned to intravitreal triamcinolone injection may receive (but is not required to receive) laser photocoagulation. When these criteria are met, the investigator should only provide the alternative treatment if he/she strongly believes that such alternative treatment is in the patient's best interest.

After the alternative treatment is received, subsequent retreatment with either intravitreal triamcinolone injection or laser photocoagulation is at investigator discretion.

**5.6 Other Treatments**

If, in the investigator's judgment, the study eye requires additional treatment other than laser photocoagulation or intravitreal triamcinolone injection, then the Protocol Chair should be contacted to discuss possible treatments. Anti-inflammatory topical medication may be prescribed for treatment of the study eye without Protocol Chair consultation.

**5.7 Pharmacokinetic Blood Draws (at selected sites only)**

Blood samples for pharmacokinetic analysis will be collected at selected sites. The blood samples will be collected following intravitreal injection according to the following schedule: pre-dose (day of dosing), 1 to 3 hr post-dose, 4-day safety visit, 4-week safety visit, and 4-month visit (or earlier if the patient discontinues prior to the 4-month visit). An addendum to the informed consent form or a separate informed consent form will be signed for patients participating in the pharmacokinetic study (see Appendix II for more details).

# CHAPTER 6.
# MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

## 6.1 Elevated Intraocular Pressure

Treatment of elevated intraocular pressure will be instituted whenever the intraocular pressure is >= 30 mmHg. The treatment to prescribe will be at investigator's discretion and may include referral to another ophthalmologist. If the intraocular pressure is between 22 and 30 mmHg, then the intraocular pressure should be re-measured within one month and treated if >=30 mmHg. Intraocular pressure >25 mmHg at consecutive 4-month visits should be treated. If intraocular pressure is >25 mmHg for 4 months, then a visual field should be performed to evaluate for glaucomatous damage.

## 6.2 Endophthalmitis

Diagnosis of endophthalmitis is based on investigator's judgment. Guidelines will be provided for distinguishing infectious from noninfectious endophthalmitis, but the diagnosis and management will be left to the investigator.

A culture is required prior to initiating antibiotic treatment for presumed endophthalmitis.

## 6.3 Cataract

It is expected that many study subjects in both the intravitreal triamcinolone acetonide arms and the laser photocoagulation arms will develop cataract within the study period. The decision to perform cataract surgery is left to the discretion of the investigator and the patient. Indications for cataract surgery should follow guidelines developed by the American Academy of Ophthalmology, Preferred Practice Pattern (Cataract in the Adult Eye, Anterior Segment Panel, 2001, page 15). Similar guidelines have been adopted by the Department of Health and Human Services (Medicare Program; Limitations on Medicare Coverage of Cataract Surgery, October 6, 1995).

## 6.4 Surgery for Vitreous Hemorrhage and Other Complications of Diabetic Retinopathy

It is expected that some study subjects will develop vitreous hemorrhage and/or other complications of diabetic retinopathy that may cause visual impairment. Vitrectomy for the complications of proliferative diabetic retinopathy such as vitreous hemorrhage should be delayed, if clinically feasible, because vitreous hemorrhage may resolve, obviating the need for vitrectomy. Furthermore, vitrectomy is thought to reduce the half-life of intravitreal triamcinolone acetonide such that subjects assigned to the triamcinolone acetonide treatment arms may experience reduced benefit from intravitreal triamcinolone acetonide injections following vitrectomy.

A suggested treatment plan that may be followed for eyes with vitreous hemorrhage and/or other complications of diabetic retinopathy is as follows:

1. Eyes with visually significant, non-clearing vitreous hemorrhage should have vitrectomy performed if there is no significant clearing in 3 months (Type I diabetes mellitus) and 6 months (Type II diabetes mellitus). Patients with poor visual acuity in the fellow eye should have vitrectomy sooner, as clinically indicated.
2. Eyes with traction retinal detachment involving or threatening the fovea should have vitrectomy performed as soon as clinically indicated.

3. Eyes with a combined traction-rhegmatogenous retinal detachment should have vitrectomy performed as soon as clinically indicated.

4. Eyes with extensive and progressive fibrovascular proliferation should have vitrectomy performed as soon as clinically indicated.

5. Eyes with vitreoretinal interface disease such as from a taut posterior hyaloid or an epiretinal membrane should have vitrectomy performed if the investigator believes that the primary cause of macular edema and reduced visual acuity is due to the vitreoretinal interface disease. A taut posterior hyaloid may be identified by a broad, thickened and opacified vitreous attachment to the macula. This can be noted both on clinical examination and on optical coherence tomography. Fluorescein angiography may show diffuse hyperfluoresence originating from the level of the retinal pigment epithelium or the outer retina.

### 6.5 Treatment of Macular Edema in Nonstudy Eye

If an eye that was not eligible for enrollment develops macular edema requiring treatment, the treatment will depend on the randomization group of the study eye.

- If the study eye was assigned to an intravitreal triamcinolone acetonide group, then in most cases the nonstudy eye will receive photocoagulation to avoid treating both eyes with intravitreal triamcinolone acetonide. However, if an investigator believes that there is an overriding reason to consider intravitreal triamcinolone acetonide for this eye, then the Protocol Chair should be contacted to discuss the situation.

- If the study eye was assigned to photocoagulation, then the nonstudy eye may be treated with either the 4mg study preparation of intravitreal triamcinolone acetonide or laser photocoagulation at investigator/patient discretion. A nonstudy eye treated with the study triamcinolone acetonide preparation will undergo the same adverse event monitoring as the study eye.

### 6.6 Laser Scatter (Panretinal) Photocoagulation (PRP)

PRP can be given if it is indicated in the judgment of the investigator. Patients are not eligible for this study if, at the time of randomization, it is expected that they will need PRP within 4 months. In general, PRP should not be given if the patient has less than severe NPDR. In general, PRP should be given promptly for previously untreated eyes exhibiting PDR with high-risk characteristics and can be considered for persons with non high-risk PDR or severe NPDR.

**Burn Characteristics For PRP**

| | |
|---|---|
| **Size (on retina)** | 500 microns |
| **Exposure** | 0.1 seconds recommended, 0.05 to 0.2 allowed |
| **Intensity** | mild white |
| **Distribution** | edges 1 burn width apart |
| **No. of Sessions/Sittings** | unrestricted (each session generally should be completed in <6 sittings) |
| **Nasal proximity to disk** | No closer than 500 microns |
| **Temp. proximity to center** | No closer than 3000 microns |
| **Superior/inferior limit** | No further posterior than 1 burn within the temporal arcades |
| **Extent** | Arcades (~3000 microns from the macular center) to at least the equator |
| **Min # of Final Burns:** | 1200 |
| **Wavelength** | Green or yellow *(red can be used if vitreous hemorrhage is present precluding use of green or yellow)* |

## 6.7 Diabetes Management

Diabetes management is left to the patient's medical care provider.

## 6.8 Patient Withdrawal and Losses to Follow-up

A patient has the right to withdraw from the study at any time. If a patient is considering withdrawal from the study, the principal investigator should personally speak to the patient about the reasons and every effort should be made to accommodate the patient.

The goal for the study is to have as few losses to follow-up as possible. The Coordinating Center will assist in the tracking of patients who cannot be contacted by the site. The Coordinating Center will be responsible for classifying a patient as lost to follow-up.

Patients who withdraw will be asked to have a final closeout visit at which the testing described for the outcome examination visits will be performed. Patients who have an adverse effect attributable to a study treatment or procedure will be asked to continue in follow-up until the adverse event has resolved or stabilized.

Subjects who withdraw will not be replaced.

## 6.9 Discontinuation of Study

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of three-year follow-up for all patients.

## 6.10 Contact Information Provided to the Coordinating Center

The Coordinating Center will be provided with contact information for each subject. Permission to obtain such information will be included in the Informed Consent Form. The contact information will be maintained in a secure database and will be maintained separately from the study data.

Phone contact from the Coordinating Center will be made with each patient in the first month after enrollment. Additional phone contacts from the Coordinating Center will be made if necessary to facilitate the scheduling of the patient for follow-up visits. A patient newsletter will be sent at least twice a year. A study logo item may be sent once a year.

Patients will be provided with a summary of the study results in a newsletter format after completion of the study by all patients.

**6.11 Patient Reimbursement**

The study will be paying up to a maximum of $100 per year for 3 years ($300 total) to cover travel and other visit-related expenses. If a patient has fewer than 4 visits in a year, the payment amount will be reduced by $25 for each visit fewer than 4. Payment will be made once a year from the Coordinating Center. *(Note: This payment schedule has been established so that all patients will be eligible to receive the same payment amount, regardless of treatment group or medical condition)*

**6.12 Collection of Fluid Samples from Cataract Surgery and Vitrectomy**

Aqueous and vitreous samples that are routinely extracted at the time of cataract surgery or vitrectomy and would otherwise be discarded may be obtained for laboratory analyses. Laboratory analyses may include evaluation of concentrations of triamcinolone acetonide, growth factors, enzymes, or other molecules. The collection of the fluid samples will be discussed with the patient during the informed consent process. The patient will have the option to decline collection of the fluid samples.

# CHAPTER 7.
# ADVERSE EVENTS

## 7.1 Definition

An adverse event is any untoward medical occurrence in a study patient, irrespective of whether or not the event is considered treatment-related.

## 7.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the patient, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the patient at each visit and complete all adverse event forms online. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event by determining if there is a reasonable possibility that the adverse event may have been caused by the treatment.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events will be coded using the MedDRA dictionary.

Definitions of relationship and intensity are listed on the DRCRnet website data entry form.

Adverse events that continue after the patient's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

## 7.3 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity (sight threatening)
- Is a congenital anomaly/birth defect

Unexpected adverse events are those that are not identified in nature, severity, or frequency in the current Clinical Investigator's Brochure.

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form.

The Coordinating Center will notify all participating investigators of any adverse event that is both serious and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

### 7.4 Data and Safety Monitoring Committee Review of Adverse Events

A Data and Safety Monitoring Committee (DSMC) will provide independent monitoring of adverse events. Cumulative adverse event data are semi-annually tabulated for review by the Data and Safety Monitoring Committee (DSMC). A list of specific adverse events to be reported to the DSMC expeditiously will be compiled (see Appendix I) and included as part of the DSMC Standard Operating Procedures document. Following each DSMC data review, a summary will be provided to IRBs.

# CHAPTER 8.
# STATISTICAL METHODS

The analysis plan will be detailed in a separate document and is summarized below.

## 8.1 Sample Size

The primary analysis consists of three two-group statistical comparisons of the proportions of eyes in the three treatment groups with a 15-letter or greater worsening in visual acuity from baseline (referred to below as "failure proportion").

### 8.1.1 Projected Failure Proportions

#### 8.1.1.1 Control Group

The ETDRS data can be used to estimate the failure rate for the laser photocoagulation group. The three-year outcome results for the eyes with baseline central retinal thickening and a visual acuity score <=73 letters that were assigned to immediate focal laser can be used to estimate the outcomes for patients not previously treated with macular laser photocoagulation. The four-year results for eyes in this subgroup that were retreated with laser at one year (i.e., still had macular edema meeting criteria for retreatment) can be used to estimate the three-year outcome for patients with prior macular photocoagulation.

From the ETDRS data, the 15-letter worsening rate can be estimated to be 16% at 3 years for eyes with no prior laser and 28% at 3 years for eyes with prior laser. If the worsening rate is adjusted for the estimated visual acuity distribution, the 15-letter worsening rate can be estimated to be 17% at 3 years for eyes with no prior laser and 31% for eyes with prior laser.

Based on a survey of the DRCRnet investigators, we are expecting that about two-thirds of patients will have had prior laser and one-third will not have had prior laser. Therefore, from the ETDRS data, we would estimate the 3-year failure rate to be 26% (one-third of patients with 17% rate and two-thirds with 31% rate). However, as noted below, the control group rate will be estimated at 20% to be even more conservative.

#### 8.1.1.2 Intravitreal Triamcinolone Acetonide Treatment Group

There is considerable clinical experience using intravitreal triamcinolone for DME; however, the data reported in the literature are limited and mostly consist of uncontrolled case series using a 4 mg dose of triamcinolone. The clinically meaningful deduction in the failure proportion is considered to be 50% of the 20% projected rate in the laser group, equaling 10%. Uncertainty exists as to the expected failure rate with 1 mg triamcinolone. Therefore, sample size is computed for varying failure rates for the 1 mg dose.

### 8.1.2 Sample Size Estimation

In estimating the sample size, the following assumptions have been made:

Failure Proportions: Laser group = 0.20, 4 mg Triamcinolone Group = 0.10, 1 mg Triamcinolone Group = 0.10, 0.15, 0.20

- Type 1 error rate = 0.049 (2-sided) adjusting for alpha spending of 0.001 for DSMC data review, prior to accounting for Hochberg adjustment for multiple comparisons

- Power = 90%

- The statistical power is being set at 90% for the sample size estimation of the number of patients to be enrolled. The sample size estimation is being conducted as if each patient has only one study eye. The effective power for the primary analysis which will include both eyes of patients with two study eyes is derived in section 8.1.2.1.

With these assumptions, the calculated sample size per group is 221 patients when the 1 mg triamcinolone group failure proportion is 0.10, 325 when the failure proportion is 0.15, and 265 when the failure proportion is 0.20.

The original sample size had been selected to be 265 patients (total = 795 patients for 3 groups). This sample size will provide approximately 94% power when the 1 mg triamcinolone group failure proportion is .10 and approximately 82% power when the 1 mg triamcinolone group failure proportion is .15. No adjustment is being made for losses-to-follow-up since the data of such patients will be included in the intent-to-treat analysis using the last-observation carried forward method.

**8.1.2.1 Statistical Power for Primary Analysis Including Two Study Eyes**

In the ETDRS, 74% of the patients had only one eye with central macular thickening and a visual acuity score $\leq$73 letters and 26% had both eyes meeting these criteria. If we assume that 20% of patients enrolled in this trial will have two study eyes, this increases the effective sample size of the laser group by 20% (from N=265 to N=318)) and of each triamcinolone group by 10% (from N=265 to N=291).

With this sample size (318 eyes in laser group and 291 eyes in triamcinolone group) and using the same assumptions listed above for the sample size estimation, statistical power is 97% for a 1 mg group failure rate of 0.10, 87% for a 1 mg failure rate of 0.15, and 92% for a 1 mg failure rate of 0.20.

**8.2 Efficacy Analysis Plan**

There will be two analyses: an "intent-to-treat" analysis and a "per-protocol" analysis.

The intent-to-treat analysis will include all randomized eyes. The last-observation-carried forward method will be used to impute data for patients who do not complete the 3-year exam.

The per-protocol analysis will be performed including only patients who complete the 3-year exam. For eyes that received the alternate treatment (laser or triamcinolone) from the randomly assigned treatment, data will be included in the analysis from the last visit prior to the administration of the alternate treatment.

If the intent-to-treat and per-protocol analyses yield the same results, the intent-to-treat analysis will be considered the definitive analysis and the per-protocol analysis will be used to provide supportive evidence of the magnitude of treatment effect among patients who received the treatment. However, if the results of the two methods differ, exploratory analyses will be performed to evaluate the factors that have contributed to the differences.

The correlation between eyes of patients who have two study eyes (one eye in the laser group and one eye in a triamcinolone group) will not be considered in the analysis. This is a

conservative approach since a positive correlation between eyes would have the effect of reducing the variance.

Pre-planned subgroup analyses will be listed in the detailed Statistical Analysis Plan.

The following principles apply to the analyses except where indicated:

1) The analyses will involve comparisons of the 1 mg and 4 mg triamcinolone groups with the laser group and with each other. A Hochberg adjustment will be used to account for the multiple statistical comparisons (as described in the Statistical Analysis Plan).

2) Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in regression models by including the following baseline covariates related to the patient (age) and study eye (visual acuity, retinal thickening on OCT, prior macular photocoagulation). Additional variables that are associated with the outcome will be included if there is an imbalance in the variables between groups.

3) The correlation between eyes of patients who have two study eyes (one eye in the laser group and one eye in a triamcinolone group) will not be considered in the analysis. This is a conservative approach since a positive correlation between eyes would have the effect of reducing the variance.

### 8.2.1 Visual Acuity

Visual acuity is the primary outcome variable. The primary outcome is a 15-letter or greater worsening in visual acuity from baseline to 3 years (failure). The primary analysis will be three two-group comparisons of the failure proportions in the treatment groups using Fisher's exact tests.

Since the primary outcome analysis is not fully assessing the primary outcome variable, additional analyses will be conducted on the visual acuity data to assess for consistency with the primary analysis. The additional analyses will include the following:

- The 3-year logMAR visual acuity scores in the three groups will be compared in an analysis of covariance model.
- The success proportions (improvement from baseline of 15 or more letters) will be compared using Fisher's exact tests and in a logistic regression model.
- For the 3-level variable of improved (change from baseline $\geq$+10 or more letters), stable (change from baseline between –9 and +9 letters), or worse (change from baseline $\leq$-10 letters), the treatment groups will be compared using a polychotomous logistic regression model.

### 8.2.2 Retinal Thickening

Change in retinal thickening will be a second outcome measure of importance. This assessment is made from gradings of the OCT central subfield and of the central and 4 inner subfields combined (the inner zone) by the Fundus Photography Reading Center. The analysis of the OCT data will be used to assist in the interpretation of the primary visual acuity analysis. A conclusion about the efficacy of treatment will not be made from the OCT results separate from the visual acuity results.

For each eye, the percent change in OCT central retinal thickening from baseline will be computed. A treatment group comparison will be performed using an analysis of covariance model.

The proportions of patients in the treatment groups for whom the DME is considered to have resolved (OCT central retinal thickness <225 microns) will be compared among groups using Fisher's exact tests and in a logistic regression model.

### 8.2.3 Composite Outcome

Visual acuity and retinal thickening (OCT) will be combined into the following composite outcome variables: (1) improvement in visual acuity of 10 or more letters and reduction calculated in retinal thickening on OCT by more than 50%, (2) improvement in visual acuity of 15 or more letters and resolution of DME on OCT (retinal thickness in central subfield <225 microns), and (3) stable or improved visual acuity (change from baseline ≥-4 letters) and resolution of DME on OCT.

Treatment group comparisons for each variable will be conducted using Fisher's exact tests.

### 8.2.4 Fundus Photographs

Fundus photographs will provide gradings of retinal thickening, hard exudate, and retinopathy severity. Change in these measures between baseline and follow-up visits will be assessed and compared by treatment group.

### 8.2.5 Formal Interim Efficacy Analyses

No formal interim efficacy analysis for the 3-year primary outcome is planned, and there is no scenario envisioned for which such an analysis would be needed.

Nevertheless, 0.0001 of alpha will be assigned for each DSMC data review, resulting in an adjustment of the final alpha from 0.05 to 0.049, prior to employing the Hochberg adjustment. DSMC procedures are detailed in Appendix I.

## 8.3 Safety Analysis Plan

The plans for review of the data by the Data and Safety Monitoring Committee is described in Appendix I.

Safety outcomes that will be assessed include:

1) Visual acuity decrease of 20 or more letters at any visit within the first 4 weeks after an intravitreal injection or laser treatment
2) Retinal detachment at any time
3) Endophthalmitis at any time (defined as any patient treated for infectious endophthalmitis regardless of whether a culture is positive): frequency of culture-positive and culture-negative cases will be reported
4) Pseudoendophthalmitis at any time (defined based on investigator diagnosis and patient not treated for infectious endophthalmitis)
5) Elevated intraocular pressure/glaucoma
6) Cataract/cataract surgery
7) Retinal vascular occlusion or anterior ischemic optic neuropathy at any time

The first safety outcome listed above (visual acuity decrease of 20 or more letters within 4 weeks of treatment) could occur from either laser treatment or an intravitreal injection. The rest of the listed safety outcomes are pertinent only in the intravitreal triamcinolone groups. However, the eyes in the laser group will provide point estimates for glaucoma, cataract, and cataract surgery that will be useful estimates of the expected incidences in the absence of treatment.

For events pertinent to both the laser and intravitreal triamcinolone treatments, the frequency of each event will be tabulated for each of the three groups and each triamcinolone group will be compared with the laser group and with each other on the basis of an adverse event occurring any time during follow-up using Fisher's exact tests. Each adverse event type will be tabulated according to the number of treatments received and according to the time point of occurrence.

For events pertinent only to the intravitreal triamcinolone groups, the frequency of each event will be tabulated for the 1 mg and 4 mg triamcinolone groups and compared using Fisher's exact tests. For the statistical assessment of these events and any other adverse event data collected at the 4-day and 4-week post-injection visits, the expected control group rate will be considered to be zero.

All systemic and other ocular adverse events will be categorized with frequencies reported by treatment group.

Further definitions of the events for analysis and the analytic approach will be provided in the detailed statistical analysis plan.

**8.4 Additional Tabulations and Analyses**

The following will be tabulated according to treatment group:

1) Baseline demographic and clinical characteristics
2) Visit completion rate for each visit
3) Protocol deviations
4) Number of protocol treatments received
5) 1-year, 2-year, and 3-year HbA1c levels

Separate analyses will be conducted for patients with one study eye and two study eyes

# REFERENCES


1. Klein R, Klein B, Moss S, Davis M, DeMets D. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, IV: diabetic macular edema. Ophthalmology 1984; 91:1464-1474.
2. Moss S, Klein R, Klein B. Ten-year incidence of visual loss in a diabetic population. Ophthalmology 1994; 101:1061-70.
3. Moss S, Klein R, Klein B. The 14-year incidence of visual loss in a diabetic population. Ophthalmology 1998; 105:998-1003.
4. Ferris F, Patz A. Macular edema: a complication of diabetic retinopathy. Surv Ophthalmol 1984; 28 (suppl):452-61.
5. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: ETDRS report number 4. Int Ophthalmol Clin 1987; 27:265-72.
6. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS report number 1. Arch Ophthalmol 1985; 103:1796-1806.
7. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report number 9. Ophthalmology 1991; 98:766-85.
8. Diabetes Control and Complication Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977-986.
9. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. UKPDS 33. Lancet 1998; 352:837-853.
10. The Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; 342:381-389.
11. Lewis H, Abrams G, Blumenkranz M, Campo R. Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction. Ophthalmology 1992; 1992:753-9.
12. Harbour J, Smiddy W, Flynn HJ, Rubsamen P. Vitrectomy for diabetic macular edema associated with a thickened and taut posterior hyaloid membrane. Am J Ophthalmol 1996; 121:405-13.
13. Tachi N, Ogina N. Vitrectomy for diffuse macular edema in cases of diaberic retinopathy. Am J Ophthalmol 1996; 122:258-60.
14. Pendergast S, Hassan T, Williams G, et al. Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid. Am J Ophthalmol 2000; 130:178-186.
15. Ikeda T, Sato K, Katano T, Hayashi Y. Vitrectomy for cystoid macular edema with attached posterior hyaloid membrane in patient with diabetes. Br J Ophthalmol 1999; 83:12-4.
16. Yamamoto T, Akabane N, Takeuchi S. Vitrectomy for diabetic macular edema: the role of posterior vitreous detachment and epimacular membrane. Am J Ophthalmol 2001; 132:369-77.
17. Antcliff R, Marshall J. The pathogenesis of edema in diabetic maculopathy. Semin Ophthalmolo 1999; 14:223-32.
18. Aiello L, Bursell S, Clermont A, et al. Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective beta-isoform-selective inhibitor. Diabetes 1997; 46:1473-80.

19. Antonetti D, Barber A, Hollinger L, Wolpert E, Gardner T. Vascular endothelial growth factor induces rapid phosphorylation of tight junction proteins occludin and zonula occluden. J Bio Chem 1999; 274:23463-7.
20. Senger D, Galli S, Dvorak A, Peruzzi C, Harvey V, Dvorak H. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 1983; 219:983-5.
21. Vinores S, Youssri A, Luna J, et al. Upregulation of vascular endothelial growth factor in ischemic and non-ischemic human and experimental retinal disease. Histol Histopathol 1997; 12:99-109.
22. Nauck M, Karakiulakis G, Perruchoud A, Papakonstantinou E, Roth M. Corticosteriods inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. Euro J Pharmacol 1998; 341:309-15.
23. Nauck M, Roth M, Tamm M, et al. Induction of vascular endothelial growth factor by platelet-activating factor and platelet-derived growth factor is downregulated by corticosteroids. Am J Resp Cell Mol Biol 1997; 16:398-406.
24. Martidis A, Duker J, Greenberg P, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002; 109:920-7.
25. Jonas J, Sofker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. Am J Ophthalmol 2001; 132:425-7.
26. Folkman J, Ingber D. Angiostatic steroids. Method of discovery and mechanism of action. Ann Surg 1987; 206:374-83.
27. Diaz-Florez L, Gutierrez R, Varela H. Angiogenesis: an update. Histol Histopathol 1994; 9:807-43.
28. Yoshikawa K, Kotake S, Ichiishi A, Sasamoto Y, Kosaka S, Matsuda H. Posterior sub-Tenon injections of repository cortisteroids in uveitis patients with cystoid macular edema. Jap J Ophthalmol 1995; 39:71-6.
29. Thach A, Dugel P, Flindall R, Sipperley J, Sneed S. A comparison of retrobulbar versus sub-Tenon's corticosteroid therapy for cystoid macular edema refractory to typical medications. Ophthalmology 1997; 104:2003-8.
30. Tano Y, Chandler D, Machemer R. Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide. Am J Ophthalmol 1980; 90:810-6.
31. Machemer R, Sugita G, Tano Y. Treatment of intraocular proliferations with intravitreal steroids. Tr Am Ophth Soc 1979; 77:177-8.
32. Antoszyk A, Gottlieb J, Machemer R, Hatchell D. The effects of intravitreal triamcinolone acetonide on experimental pre-retinal neovascularization. Graefes Arch Clin Exp Ophthalmol 1993; 231:34-40.
33. Danis R, Bingaman D, Yang Y, Ladd B. Inhibition of preretinal and optic nerve head neovascularization in pigs by intravitreal triamcinolone acetonide. Ophthalmology 1996; 103:2099-2104.
34. Jonas J, Hayler J, Panda-Jones S. Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy. Br J Ophthalmol 2000; 84:1064-7.
35. Penfold P, Gyory J, Hunyor A, Billson F. Exudative macular degeneration and intravitreal triamcinolone. A pilot study. Aust N Z J Ophthalmol 1995; 23:293-8.
36. Challa J, Gillies M, Penfold P, Gyory J, Hunyor A. Exudative macular degeneration and intravitreal triamcinolone: 18 month follow up. Aust N Z J Ophthalmol 1998; 26:277-81.
37. Danis R, Ciulla T, Pratt L, Anliker W. Intravitreal triamcinolone acetonide in exudative age-related macular degeneration. Retina 2000; 20:244-50.

38. Armaly M. Statistical attributes of the steroid hypertensive response in the clinically normal eye. Invest Ophthalmol Vis Sci 1965; 4:187-97.
39. Becker B. Intraocular pressure response to topical corticosteroids. Invest Ophthalmol Vis Sci 1965; 4:198-205.
40. Goldberg I. Ocular inflammatory and corticosteroid-induced glaucoma. In Ophthalmology 1999:12.17.1-12.17.6.
41. Jonas J, Kreissig I, Sofker A, Degenring R. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol 2003; 121:57-61.
42. Cumming R, Mitchell P, Leeder S. Use of ingaled corticosteroids and the risk of cataracts. N Engl J Med 1997; 337:8-14.
43. Butcher J, Austin M, McGalliard J, Bourke R. Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. BMJ 1994:309-43.
44. Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroids use with cataract extraction in elderly patients. JAMA 1998; 280:539-43.
45. Aaberg Jr T, Flynn Jr H. Nosocomial postoperative endophthalmitis. Invest Ophthalmol Vis Sci 1996; 37:S775.
46. Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antobiotics for the treatment of postoperative bacterial endophthalmitis. Arch Ophthalmol 1995; 113.
47. Hida T, Chandler D, Arena J, Machemer R. Experimental and clinical observations of the intraocular toxicity of commercial corticosteroid preparations. Am J Ophthalmol 1986; 101:190-5.
48. Roth D, J C, MJ S, SN G, DL Y, Chaudhry NA. Noninfectious endophthalmitis associated with intravitreal triamcinolone injection. Arch Ophthalmol 2003; 121:1279-82.
49. Sutter F, Gillies M. Pseudo-endophthalmitis after intravitreal injection of triamcinolone. Br J Ophthalmol 2003; 87:972-4.
50. McCuen B, Bressler N, Tano Y, Chandler D, Machemer R. The lack of toxicity of intravitreally administered triamcinolone acetonide. Am J Ophthalmol 1981; 91:785-8.
51. Massin P, Audren F, Haouchine B, al e. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema. Ophthalmology 2004; 111:218-225.
52. Wingate R, Beaumont P. Intravitreal triamcinolone and elevated intraocular pressure. Aust N Z J Ophthalmol 1999; 27:431-2.
53. Jonas J, Hayler J, Sofker A, Panda-Jones S. Regression of neovascular iris vessels by intravitreal injection of crystalline cortisone. J Glaucoma 2001; 10:284-7.
54. Bergh F. Binding characteristics of the glucocorticoid receptor in peripheral blood lymphocytes in multiple sclerosis. J Neurol 1999; 246:292-8.
55. Schottelius A. Higher expression of glucocorticoid receptor in peripheral mononuclear cells in inflammatory bowel disease. Am J Gastroenterol 1994; 95:2000.
56. Beck RW, Moke PS, Turpin AH, Ferris FL, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. Am J Ophthalmol 2003; 135:194-205.

# APPENDIX I

## Monitoring Plan for the Data and Safety Monitoring Committee for Intravitreal Triamcinolone Acetonide for DME Protocol

### 1. General Considerations

The Data and Safety Monitoring Committee (DSMC) has the responsibility for reviewing the ethical conduct of the trial and monitoring patient safety. In addition, the committee will have a role in the 1-year and 3-year efficacy analyses. Prior to the initiation of recruitment for the trial, the DSMC must approve the study protocol and informed consent form. Subsequent protocol changes that are substantive must be approved by the DSMC prior to implementation. Minor changes that do not impact on patient safety or the assessment of efficacy do not require prior DSMC approval and will be reported to the DSMC at its meetings.

The DSMC consists of two biostatisticians (one of whom serves as chair), three diabetic retinopathy specialists, a diabetologist, and a layperson who serves as a patient advocate. It will also include a representative of the National Eye Institute (NEI) as ex-officio (nonvoting) member.

### 2. DSMC Review of Adverse Events and Monitoring for Safety

Certain adverse events will require expedited reporting to the DSMC. These will be reported in the form of a capsule summary to a designated member of the committee. The member will review the case and if he believes it is indicated, a conference call of the full committee will be convened. The events for expedited reporting will include (1) deaths from any cause, (2) any life-threatening events related to a study treatment or procedure, and (3) the occurrence of any of the following:

- Loss of 20 or more letters at any visit within the first 4 weeks after an intravitreal injection or laser treatment
- Retinal detachment at any time
- Endophthalmitis at any time (defined as any patient treated for endophthalmitis regardless of whether a culture is positive)
- Intraocular pressure >35 mmHg on maximal medical therapy and any cases receiving laser or a filtering procedure to lower the pressure.
- Retinal vascular occlusion or anterior ischemic optic neuropathy at any time.

At approximately 6-month intervals beginning approximately 12 months after the trial begins, the DSMC will review a compiled data report. The report will include a case report listing of the adverse events noted above for expedited reporting. These events and all other adverse events will be tabulated by treatment group in summary tables. Data will be provided on the lens gradings made clinically and by the Reading Center and on changes in intraocular pressure.

Visual acuity data will be reviewed by treatment group as part of the safety analysis. The committee will be provided with both categorical data on the proportions of patients with a specific change from baseline and data on the mean change from baseline so that it can assess whether there is a detrimental effect of treatment.

**3. DSMC Review of Efficacy Data and Early Stopping of the Trial**

As part of its safety data review (see section 2), the DSMC will be provided with visual acuity data by treatment group so that it can assess the risk-benefit ratio of the trial by weighing the magnitude and severity of adverse events that have occurred against any apparent benefit of treatment.

There is no scenario envisioned for which the trial will be stopped early for efficacy. First, primary outcome data (3-year visual acuity) will not begin to be accrued until late in the trial. Second, there is considerable concern about the long-term safety of multiple intravitreal triamcinolone acetonide injections. Regardless of how strong the data prior to three years is indicative of efficacy, there is an overriding need for the trial to go to its conclusion so that the long-term risk-benefit ratio can be assessed.

There is also no scenario envisioned for which the trial will be stopped early for safety. If substantial safety concerns occur, it is possible that the DSMC could recommend that additional patient enrollment cease and that the enrolled patients not receive further intravitreal injections. However, the study can be expected to continue for the enrolled patients.

**4. Alpha Spending**

As noted in section 3, there is no plausible scenario for which the trial will be stopped early for efficacy. Therefore, formal interim efficacy analyses are not being planned. Nevertheless, a minimal amount of alpha spending (0.0001) will be allocated for each DSMC review of the data. There are projected to be six DSMC data reviews that will contain treatment group comparisons prior to the end of the trial. The final alpha level at the end of the trial will be accordingly adjusted to 0.049 for the overall statistical comparisons of the three treatment groups.

**5. Study Timeline and DSMC Data Reviews**

The table below indicates each time point for the review of study data by the DSMC.

## Study Timeline for DSMC Data Reviews

| | Enrollment | 4mo FU | 1yr FU | 2yr FU | 3yr FU | DSMC Mtg |
|---|---|---|---|---|---|---|
| | | | | | | |
| **2004** May | | | | | | |
| June | X | | | | | |
| July | X | | | | | |
| August | X | | | | | |
| September | X | | | | | |
| October | X | X | | | | |
| November | X | X | | | | x* |
| December | X | X | | | | |
| **2005** January | X | X | | | | |
| February | X | X | | | | |
| March | X | X | | | | |
| April | X | X | | | | |
| May | X | X | | | | x |
| June | X | X | X | | | |
| July | X | X | X | | | |
| August | X | X | X | | | |
| September | | X | X | | | |
| October | | X | X | | | |
| November | | X | X | | | x |
| December | | X | X | | | |
| **2006** January | | | X | | | |
| February | | | X | | | |
| March | | | X | | | |
| April | | | X | | | |
| May | | | X | | | x |
| June | | | X | X | | |
| July | | | X | X | | |
| August | | | X | X | | |
| September | | | | X | | |
| October | | | | X | | |
| November | | | | X | | x |
| December | | | | X | | |
| **2007** January | | | | X | | |
| February | | | | X | | |
| March | | | | X | | |
| April | | | | X | | |
| May | | | | X | | x |
| June | | | | X | X | |
| July | | | | X | X | |
| August | | | | X | X | |
| September | | | | | X | |
| October | | | | | X | |
| November | | | | | X | x |
| December | | | | | X | |
| **2008** January | | | | | X | |
| February | | | | | X | |
| March | | | | | X | |
| April | | | | | X | |
| May | | | | | X | x |
| June | | | | | X | |
| July | | | | | X | |
| August | | | | | X | |

***insufficient data to tabulate by treatment group**

# APPENDIX II

## Pharmacokinetic Blood Draws for Therapeutic Drug Monitoring
*(at selected sites only)*

***Number of Patients***

Approximately 40 patients from the 1mg and 4mg intravitreal triamcinolone acetonide treatment groups (at selected sites) will have blood drawn at specified visits for measuring plasma triamcinolone acetonide concentrations.

| Treatment Group | Number of PK Patients |
|---|---|
| Standard of Care | 0 Patients |
| 1mg of Intravitreal Triamcinolone Acetonide | 20 Patients (approx. 10 M / 10 F) |
| 4mg of Intravitreal Triamcinolone Acetonide | 20 Patients (approx 10 M / 10 F) |

***PK Sampling Timepoints***

Blood samples will be collected following intravitreal injection according to the following schedule: pre-dose (day of dosing), 1 to 3 hr post-dose, 4-day post-dose visit (anytime), 4-week post-dose visit (anytime), and 4-month post-dose visit (or earlier if the patient discontinues prior to the 4-month visit)

***Bioanalysis***

Plasma triamcinolone acetonide concentrations will be measured using a validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS). The bioanalysis of triamcinolone acetonide will be conducted at Allergan (Irvine, CA).

***Data Analysis***

The summary statistics will be calculated for plasma triamcinolone acetonide concentrations.

***Process, Handling and Shipment of Pharmacokinetic Samples***

Refer to the DRCRnet Study Procedures Manual.