# Diabetic Retinopathy Clinical Research Network

# A Pilot Study of Peribulbar Triamcinolone Acetonide for Diabetic Macular Edema

**Version 1.2**

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# CHAPTER 1.
# BACKGROUND AND PROTOCOL SYNOPSIS

## 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. However, use of intravitreal corticosteroids generally has been reserved for cases of DME in which there is at least moderate loss of visual acuity (e.g., worse than 20/40). This treatment generally has not been widely used for mild cases of DME due to concerns about its potential risks, particularly glaucoma and cataract, relative to the potential benefit.

Injection of corticosteroids around the eye (anterior subtenon's, posterior subtenon's, retrobulbar) has been used as an alternative to intravitreal injection. Although data are limited, it is presumed that the adverse effects on the eye are lower with an injection around the eye compared with in the eye. There are also little data on the efficacy of this treatment. This study is being conducted to collect pilot data on the safety and efficacy of peribulbar corticosteroids to determine whether there is sufficient evidence of efficacy to merit conducting a phase 3 randomized trial.

### 1.1.2 Rationale for Peribulbar Corticosteroid 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.

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.[24, 25] 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.[26] In animal studies, intravitreal triamcinolone acetonide has been used in the prevention of proliferative vitreoretinopathy[27, 28] and retinal neovascularization.[29, 30] Intravitreal triamcinolone acetonide has been used clinically in the treatment of proliferative vitreoretinopathy[31] and choroidal neovascularization.[32-34]

### 1.1.3 Clinical Experience

There is substantial clinical experience with using peribulbar/retrobulbar corticosteroids to treat uveitis and post-cataract extraction cystoid macular edema although no definitive clinical trials have been done. The use of this treatment for the diabetic macular edema has been less extensive. We are not aware of any prospective studies that have been published with regard to peribulbar/retrobulbar corticosteroids for DME. Ohguro et al [35] has reported on the treatment of six eyes that had persistent DME after vitrectomy with a posterior subtenon's injection of 12 mg of triamcinolone. Retinal thickening decreased and visual acuity improved in three of the six eyes.

Posterior subtenon's injections of 40 mg of triamcinolone have been used to treat DME at the Cleveland Clinic for a number of years (Peter Kaiser, personal communication). An unpublished retrospective study of 63 eyes with persistent DME following at least one session of focal laser found improvement of visual acuity of 3 or more lines in 21% of eyes at 12 months. Elevation of intraocular pressure occurred transiently in 3 patients. Ptosis occurred in 2 patients. An unpublished subsequent trial of 72 eyes randomized to either laser or a 40 mg subtenon's triamcinolone injection found that 26% of the triamcinolone group and none of the laser group had a 3 or more line improvement in visual acuity at 12 months. Intraocular pressure rose 10 mm Hg or more in 2 eyes in the triamcinolone group and none in the laser group, cataract progressed in 5 eyes in the triamcinolone group and in 1 eye in the laser group, and ptosis occurred in 2 eyes in the triamcinolone group and none in the laser group.

Although the posterior subtenon's, peribulbar or retrobulbar approach has been mainly used for triamcinolone injections, Karl Csaky of the National Eye Institute has been experimenting with anterior subtenon's injections of triamcinolone. Dr. Csaky has demonstrated in rabbits that were given an anterior subtenon's injection of gadolinium that transcleral penetration of gadolinium occurs primarily through an anterior scleral-uveal inflow pathway. It is not known whether this

same effect would be seen in the human eye or with triamcinolone. However, in clinical cases of DME, Dr. Csaky has demonstrated that an anterior subtenon's injection of 20 mg of triamcinolone can substantially reduce the DME. The anterior injection is simple and carries less potential risk than a posterior injection. It is possible, however, that an anterior injection could be associated with a higher incidence of IOP elevation than a posterior injection. A 0.5 cc volume is about the maximum that can be given through an anterior subtenon's injection.

**1.2 Study Objectives**

This pilot study is being conducted to collect data that can be used to determine whether a phase 3 randomized trial should be conducted, and if it is to be conducted, to provide information to help design the protocol and to estimate sample size.

The specific objectives are as follows:

- To estimate the incidence of improvement of DME following a posterior peribulbar 40 mg triamcinolone acetonide injection compared with laser
- To estimate the incidence of improvement of DME following an anterior peribulbar 20 mg triamcinolone acetonide injection compared with laser
- To estimate the incidence of intraocular pressure elevation and other complications with each type of injection
- To provide preliminary data comparing the incidence of improvement of DME with a peribulbar triamcinolone alone versus peribulbar triamcinolone followed by laser photocoagulation

**1.3 Study Design and Synopsis of Protocol**

**A. Study Design**

- Phase 2 randomized, multi-center clinical trial.

**B. Major Eligibility Criteria**

- Age >=18 years.
- At least one eye meeting the following criteria;
  - Best corrected E-ETDRS acuity >= 69 letters
  - Retinal thickening due to DME based on clinical exam and a thickness of 250 microns or more in the central subfield on OCT
  - Maximal laser, defined as the investigator believing that additional laser treatment will provide the patient an opportunity for an improvement in visual acuity, has not already been given and investigator believes that either peribulbar steroids or laser may benefit the eye

**C. Treatment Groups**

100 patients will be randomized. A minimum of 40 eyes will be randomized that have not received prior laser (or other treatment) for DME

Patients with One Study Eye will be randomized with equal probability to one of five treatment groups

- Focal laser photocoagulation (modified ETDRS technique)

- Posterior peribulbar injection of 40 mg triamcinolone (Kenalog)
- Anterior peribulbar injection of 20 mg triamcinolone
- Posterior peribulbar injection of 40 mg triamcinolone followed after one month by laser
- Anterior peribulbar injection of 20 mg triamcinolone followed after one month by laser

Patients with Two Study Eyes
One eye randomly assigned to laser and the other eye randomly assigned to one of the four triamcinolone groups.

**D. Follow-up Schedule**

- 4 weeks (1 month)
- 8 weeks (2 months)
- 17 weeks (4 months)
- 34 weeks (8 months)
- 1 year
- 2 years
- 3 years

**E. Retreatment**

A second injection may be given at any visit beginning with the 4 month visit

*Primary criterion for retreatment is central subfield thickness >=250 microns.*

**F. Follow-up Schedule and Protocol after 8 Months**

Treatment and follow up schedule at investigator discretion
Data form completed once a year through 3 years (principal interest: glaucoma/cataract)

**G. Examination Procedures**

The following procedures will be done on both eyes at baseline and at each scheduled visit unless otherwise specified:

- E-ETDRS visual acuity (refraction at baseline, 8 months, 2 years, 3 years)
- OCT
- Fundus Photographs (7-field at baseline, 8 months, 24 months, and 36 months; 3-field at 4 months and 12 months; no photos at 1 month and 2 months)
- Intraocular pressure measurement
- Cataract assessment (baseline, 4 months, 8 months, and annual)
- Fluorescein angiogram at baseline if part of usual care (study eye only). If performed at baseline, repeated at 4 months.

**E. Main Efficacy Outcomes**

Primary

- Visual acuity (measured with E-ETDRS)

Secondary

- Retinal thickening measured on OCT
- Persistence/recurrence of DME either retreated or meeting criteria for retreatment during the first 8 months
- Change in area of retinal thickening and in threat to/involvement of the center of macula (estimated in color photographs)

## F. Main Safety Outcomes

- Intraocular pressure elevation/glaucoma
- Cataract
- Ptosis
- Complications of injection procedure

## G. Schedule of Study Visits and Examination Procedures

| | Study Month | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **0** | **1** | **2** | **4** | **8** | **12** | **24** | **36** |
| E-ETDRS visual acuity[a] | x | x | x | x | x | x | x | x |
| Fundus photos | 7F | | | 3F | 7F | 3F | 7F | 7F |
| OCT | x | x | x | x | x | x | x | x |
| IOP | x | x | x | x | x | x | x | x |
| Eye Exam[b] | x | x | x | x | x | x | x | x |
| Blood pressure | x | | | | | x | x | x |
| HbA1c[c] | x | | | x | x | x | x | x |
| Fluor. Angio[d] | x | | | x | | | | |

Eye Exam and Fluorescein Angiography are done on the study eye only; all other procedures are performed on both eyes.

a=includes protocol refraction at 0, 8 months, 24 months, 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.

b=includes lens assessment using standard photos at 0, 4, 8, 12, 24, and 36 months (selected sites will obtain lens photos with Neitz and slit lamp cameras)

c=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)

d=does not need to be performed if not part of usual care. If performed at baseline, repeat at 4 months.

# CHAPTER 2.
# SUBJECT ELIGIBILITY AND ENROLLMENT

## 2.1 Identifying Eligible Subjects and Obtaining Informed Consent

Enrollment will include approximately 100 patients A minimum of 40 eyes will be randomized that have not received prior laser (or other treatment) for DME. It is expected that recruitment will include 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 treatment groups.

## 2.2 Patient Eligibility Criteria

### 2.2.1 Subject-level Criteria

Inclusion

***To be eligible, the following inclusion criteria (1-4) 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. Able and willing to provide informed consent.

Exclusion

***A patient is not eligible if any of the following exclusion criteria (5-13) are present:***

5. History of chronic renal failure requiring dialysis or kidney transplant.
6. 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.*
7. 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.
8. Known allergy to any corticosteroid or any component of the delivery vehicle.
9. 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.
10. History of steroid-induced intraocular pressure elevation that required IOP-lowering treatment in either eye.
11. Warfarin (coumadin) currently being used.
12. 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.*
13. Patient is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the next 8 months.

### 2.2.2 Study Eye Criteria

The patient must have at least one eye meeting all of the inclusion criteria (a-e) and none of the exclusion criteria (f-t) 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 >= 69 letters (i.e., 20/40 or better).
b. Definite retinal thickening due to diabetic macular edema based on clinical exam.
c. Retinal thickness in the OCT central subfield measuring 250 microns or more
d. Maximal laser has not already been given and investigator believes that either peribulbar steroids or laser may benefit the eye (*note: subjects may be enrolled without having received prior macular laser).*
e. Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs and OCT.

Exclusion

f. 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 intraocular surgery such as cataract surgery or (2) clinical exam and/or OCT suggests that vitreoretinal interface abnormality (e.g., a taut posterior hyaloid or epiretinal membrane) is judged to be a cause of the macular edema.*

g. 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).

h. 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.).

i. History of prior treatment with intravitreal, peribulbar, or retrobulbar corticosteroids for DME.

j. 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.*

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

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

m. History of prior vitrectomy.

n. 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.

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

p. Intraocular pressure >= 25 mmHg.

q. 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.*

r. History of prior herpetic ocular infection.

s. Exam evidence of ocular toxoplasmosis.

t. 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.

Maximum time windows from the completion of each procedure to the day of randomization have been established.

Testing will be performed on both eyes unless otherwise specified.

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.*[36]
2. OCT *(done within 21 days prior to randomization).*
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 clinical 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.*
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.

**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. Randomization is completed on the DRCRnet website.
   Patients with one study eye will be randomly assigned (stratified by prior laser) with equal probability to one of five treatment groups:

   1) Focal laser photocoagulation (modified ETDRS technique)
   2) Posterior peribulbar injection of 40 mg triamcinolone (Kenalog)
   3) Anterior peribulbar injection of 20 mg triamcinolone
   4) Posterior peribulbar injection of 40 mg triamcinolone followed after one month by laser
   5) Anterior peribulbar injection of 20 mg triamcinolone followed after one month by laser

   Patients with Two Study Eyes

   For patients with two study eyes (both eyes eligible at the time of randomization), the right eye (stratified by prior laser) will be randomly assigned with equal probabilities to one of the five treatment groups listed above. If the right eye was assigned to laser only, then the left eye will be assigned to one of the four triamcinolone groups above with equal probability (stratified by prior laser). If the right eye was assigned to receive triamcinolone, then the left eye will receive laser only.

2. 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.
3. If a patient is assigned to receive triamcinolone, treatment must be given within 7 days of randomization
4. For patients with two study eyes, each eye must be treated within 7 days of randomization (treatment of both eyes on the same day is permissible).
5. For eyes assigned to triamcinolone followed by laser, the laser will be given at the 1-month follow-up visit.

# CHAPTER 3.
# MACULAR LASER PHOTOCOAGULATION

## 3.1 Introduction

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 5.3.

## 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.
# PERIBULBAR TRIAMCINOLONE

## 4.1 Introduction

Two different triamcinolone regimens are being assessed in the study: 40 mg injected posteriorly (in the posterior subtenon's space) and 20 mg injected anteriorly (in the anterior subtenon's space if possible or subconjunctival).

The injection techniques based on investigator's standard techniques. Guidelines will be provided in the procedures manual.

The timing of, and criteria for, retreatment with peribulbar triamcinolone are detailed in section 5.3.

## 4.2 Triamcinolone Acetonide Preparation

The triamcinolone acetonide preparation to be used in the study is Kenalog.

Kenalog is made by Bristol Myers Squibb and is approved by the Food and Drug Administration for intramuscular use for a variety of indications. Peribulbar injections of Kenalog have been used for a variety of ocular conditions, particularly uveitis and post-cataract extraction cystoid macular edema, for many years. The study is being conducted under an IND as peribulbar injection is considered off-label use.

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

## 5.1 Follow-up Schedule

- 4 weeks (1 month) ± 1 week
- 8 weeks (2 months) ± 2 weeks
- 17 weeks (4 months) ± 4 weeks
- 34 weeks (8 months) ± 4 weeks
- 1 year ± 8 weeks
- 2 years ± 26 weeks
- 3 years ± 26 weeks

For eyes assigned to a triamcinolone plus laser treatment group, the laser will be given at the 4-week follow-up visit.

Additional visits may occur at any time at investigator discretion.

A visit is not considered missed until the window opens for the next visit. Therefore, every effort should be made to complete a visit even if the window has closed.

## 5.2 Examination Procedures

The following procedures will be done at each scheduled visit on both eyes unless specified.

1) E-ETDRS visual acuity (refraction required at 8 months, 2 years, 3 years)
   - 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) Intraocular pressure measurement (using Goldmann tonometer)
3) Slit lamp and dilated fundus exam (study eye only)
4) Lens assessment
   - Standard photographs will be used for the assessment of nuclear sclerosis, posterior subcapsular changes, and cortical changes at the 4 months, 8 months, and annual visits.
   - The Reading Center will assess posterior subcapsular and cortical lens changes from the reflex photographs that accompany the fundus photographs
5) OCT
   - Should be performed using the same OCT machine version used at baseline
6) Fundus photographs
   - ETDRS 7-fields (1M, 2, 3M, 4, 5, 6, 7, reflex) at the 8-month, 24 and 36 months visits and 3-fields (1M, 2, 3M, reflex) at 4 months and 12 months (no photos at 1 and 2 months)
7) Fluorescein angiogram at 4 months (study eye only), if performed at baseline as part of usual care and there is no contra-indication to performing the angiogram
8) Measurement of blood pressure.
   - Performed at 1 year, 2 year, and 3 year visits only
9) HbA1c

- Obtained as part of usual care at 4 months, 8 months, and annual visits.
- If an HbA1c test result is available from the prior 3 months, it does not need to be repeated at these visits.

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 1.3 summarizes the testing performed at each visit.

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

**5.3 Retreatment with Randomization Assigned Treatment Prior to the 8-month Visit**

In all treatment groups, the study eye is considered for retreatment with the randomized treatment at the 4-month visit.

Retreatment with the randomized treatment should be performed no sooner than 3.5 months from the previous treatment. Unless there is a contraindication to retreatment (e.g., adverse effects from the initial treatment), retreatment generally should occur if the thickness of the central subfield is >= 250 microns or if the judgment of the investigator, DME is still present that warrants retreatment.

When an eye is retreated with triamcinolone, the patient should be seen back in 4 weeks to evaluate for adverse effects (specifically to measure the intraocular pressure). Eyes assigned to triamcinolone plus laser should be retreated with laser at this visit unless further laser is contraindicated.

If retreatment is not given at the 4-month visit, the investigator can decide whether the eye should be reevaluated for retreatment sooner than the 8-month visit.

**5.4 Alternative Treatments Prior to the 8-month Visit**

During the first 8 months, if visual acuity in the study eye has decreased by 15 or more letters from baseline (replicated after a repeat refraction), then any treatment may be given at investigator discretion. Otherwise, during the first 30 weeks, an eye should receive only the protocol assigned treatment.

If, in the investigator's judgment, the study eye requires additional treatment during the first 8 months other than the protocol assigned treatment, 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.

**5.5 Treatment after the 8-month Visit**

After completion of the 8-month visit, treatment is at investigator discretion.

# CHAPTER 6.
# MISCELLANEOUS CONSIDERATIONS

## 6.1 Elevated Intraocular Pressure

Treatment of elevated intraocular pressure will be instituted whenever the intraocular pressure is >= 30 mmHg at one visit or >25 mm Hg for 4 months or more. The treatment to prescribe will be at investigator's discretion and may include referral to another ophthalmologist.

## 6.2 Cataract

If a cataract develops, 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).

## 6.3 Treatment of Macular Edema in Nonstudy Eye

Treatment of the nonstudy eye is left to the discretion of the investigator

## 6.4 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)* |

## 6.5 Diabetes Management

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

## 6.6 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 Coordinating Center should be contacted prior to formally withdrawing the patient from the study. Ownership of the data collected up until the time of withdrawal is retained by the DRCR Network.

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 close-out 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, if not resolved or stabilized at the time of the final study visit.

Subjects who are determined to be ineligible or for whom there are substantial deviations from the protocol may be discontinued from the study.

Subjects who withdraw will not be replaced.

## 6.7 Participation in Other Studies Prior to the End of Three-year Follow-up

The Steering Committee may decide (with concurrence of the Data and Safety Monitoring Committee) to permit patients to participate in a new DRCR.net or other study after the first 30 weeks of follow up. If the patient enters another research study, data will still be collected during Phase 2 of this current study.

## 6.8 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.

## 6.9 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.

### 6.10 Patient Reimbursement

The study will be paying $25 per completed visit for the 4 scheduled follow-up visits during the first 8 months and for the three annual visits (7 visits= maximum payment of $175) to cover travel and other visit-related expenses. Payment will not be made for missed visits. Payment will be made by the Coordinating Center once after the first 8 months and then after each annual visit. If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses.

### 6.11 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 drug being used in the study is FDA-approved and there is not a study-specific Clinical Investigator Brochure.

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

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.

Subjects will not be masked to whether they have been assigned to a laser or peribulbar triamcinolone group; however, they will be masked to assignment to the 20 mg and 40 mg triamcinolone groups. Investigators will not be masked to treatment group. Visual acuity testing will be performed with the computerized electronic ETDRS procedure, which minimizes potential subject bias and nearly eliminates potential technician bias; nevertheless, attempts will be made to have the technician masked when possible. The Reading Center, which will grade the OCTs and fundus photographs, will be masked to treatment group assignment. The data analyst will not be masked to treatment group (this is not viewed as a potential source of bias for this protocol).

# 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 Package Insert.

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). The DSMC Standard Operating Procedures document provides details of the committee's role in review of adverse events and in other aspects of the study. Following each DSMC data review, a summary will be provided to the sites to submit to IRBs.

# CHAPTER 8.
# STATISTICAL METHODS

The approach to sample size estimation and the general statistical analysis plan are summarized below and will be detailed in a separate Statistical Analysis Plan.

## 8.1 Sample Size and Statistical Power

A convenience sample of 20 subjects per group will be randomized. As a phase II study this protocol aims to determine if a trend exists and if the trend is strong enough to warrant a phase III trial. Statistical power to detect a difference between groups in the visual acuity outcome will approach zero. If a true benefit of treatment exists, statistical power for the secondary outcomes is expected to be higher than it will be for visual acuity.

## 8.2 Statistical Analyses

This protocol is aimed at hypothesis generating. As a phase II study the analysis will consist of estimation of the event rate for several outcomes. In addition, the analysis will compare the effect of the different treatment groups on several outcomes at four time points to describe trends and determine if a phase III trial is warranted.

Eight months of follow up has been selected as the time point for the primary analysis. Secondary analysis will be conducted at 1 month, 2 months, and 4 months. Since following the eight-month outcome exam the patient is no longer restricted to the randomized treatment, analysis on subsequent visits will be interpreted with caution. Analyses of post 8-month visit data will focus on safety.

### 8.2.1 Outcome Estimates

One of the goals of this study is to obtain estimates of important efficacy and safety outcomes for each of the treatment groups. This will provide a basis for sample size estimation and hypothesis generation in a phase III trial. Estimates for the following outcomes will be calculated for each treatment group and exact 95% confidence intervals will be constructed where applicable.

**Efficacy:**

**Visual Acuity**

- Worsening in visual acuity >= 15 letters (primary)
- Mean change in visual acuity from baseline
- Visual acuity – "improved" (change from baseline $\geq$+10 or more letters), "stable" (change from baseline between –9 and +9 letters), "worse" (change from baseline $\leq$-10 letters).

**OCT**

- Reduction in retinal thickening in central subfield by >= 50%.
- Reduction in retinal thickening in the inner zone (central and 4 inner subfields) by >= 50%.

- Reduction in retinal thickening in all subfields with baseline thickening > 3 standard deviations above normal by > 50%
- Incidence of resolution of diabetic macular edema in the central subfield (DME will be considered resolved if retinal thickening is < 50 microns).
- Distribution of change in retinal thickening.

**Other**

- Persistence/recurrence of DME meeting criteria for retreatment during the first 34 weeks
- Proportion of retreated eyes

**Safety:**

- Proportion of eyes with IOP >= 30 mmHg at any time during the study
- Proportion of eyes with an increase in IOP from baseline >=10 mmHg at any time during the study
- Incidence of glaucoma (filter or laser)
- Incidence of cataract extraction
- The proportion of patients with posterior subcapsular or cortical cataract, both types of opacities, or either type (as assessed by the reading center) not present at baseline.
- The proportion of patients with nuclear sclerosis, posterior subcapsular, and/or cortical opacities (on investigator assessment) increased from baseline.
- Incidence of ptosis
- Incidence of complication related to the injection procedure.

### 8.2.2 Treatment Group Comparisons

The following treatment group comparisons are of principal interest:

- Posterior peribulbar (40 mg) triamcinolone injection compared with laser.
- Anterior peribulbar (20 mg) triamcinolone injection compared with laser.
- Posterior peribulbar (40 mg) triamcinolone injection followed by laser compared with laser.
- Anterior peribulbar (20 mg) triamcinolone injection followed by laser compared with laser.
- Posterior peribulbar (40 mg) triamcinolone compared with anterior peribulbar (20 mg) triamcinolone.
- Posterior peribulbar (40 mg) triamcinolone injection only compared with posterior peribulbar (40 mg) TAC plus laser.
- Anterior peribulbar (20 mg) triamcinolone injection only compared with anterior peribulbar (20 mg) TAC plus laser.

### 8.2.3 Visual Acuity

Visual acuity is the primary outcome variable. The primary outcome will be analyzed using Fisher's exact tests. In addition, logistic regression models will be fit with the following covariates: baseline logMAR acuity, baseline central retinal thickening, indication of prior laser treatment, and age at randomization.

The following principles apply to the primary analysis:

1. The intent-to-treat analysis will include all randomized eyes
2. Primary analyses will be conducted excluding patients who missed the visit
3. The correlation between eyes of patients who have two study eyes (one eye in the laser group and one eye in either of the TAC groups) will be not be accounted for in the primary analysis.

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 follow-up logMAR visual acuity scores among the groups will be compared in an analysis of covariance model controlling for baseline acuity.
- 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.

### 8.2.4 Retinal Thickening

The assessment of retinal thickening 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. Analyses will include comparing the incidence of resolution of DME, reduction of >=50% in retinal thickening in the central subfield between the treatment groups, and the incidence of >= 50% reduction in retinal thickening in the inner zone (central subfield and 4 inner subfields) and the outer zone (all 9 subfields).

### 8.2.5 Fundus Photograph Measurements

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

### 8.2.6 Additional Outcomes

Additional analysis based on the proportion of eyes with persistent or recurrent DME, either retreated or meeting the criteria for retreatment; the proportion of retreated eyes; and time to retreatment will also be conducted.

### 8.2.7 Formal Interim Efficacy Analyses

No formal interim efficacy analysis 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 of six DSMC data review, resulting in an adjustment of the final alpha from 0.05 to 0.049.

**8.3 Safety Analysis Plan**

All subjects who received at least one study treatment (laser or TAC injection) will be included in the safety analyses.

All reported adverse events will be categorized and tabulated according to treatment group.

Specific safety outcomes of interest that will be assessed include:

1) Elevated intraocular pressure/glaucoma
2) Cataract/cataract surgery
3) Ptosis
4) Complications of injection procedure

Descriptive statistics will be provided for the five treatment groups overall and stratified by the number of injections and time point of occurrence. Point estimates and 95% confidence intervals will be provided.

The safety outcomes listed are pertinent only in the triamcinolone groups. However, the eyes in the laser group will provide point estimates that will be useful estimates of the expected incidences in the absence of treatment.

For events pertinent to both the laser and peribulbar triamcinolone treatments, the frequency of each event will be tabulated for each of the groups and the groups will be compared 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 triamcinolone groups, the frequency of each event will be tabulated and compared using Fisher's exact tests.

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