The Standard Care vs. COrticosteroid for REtinal Vein Occlusion (SCORE) Study

Two Randomized Trials to Compare the Efficacy and Safety of Intravitreal Injection(s) of Triamcinolone Acetonide with Standard Care to Treat Macular Edema: One for Central Retinal Vein Occlusion and One for Branch Retinal Vein Occlusion

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Study Chair
Michael S. Ip, MD
University of Wisconsin Medical School
Dept of Ophthalmology and Visual Sciences
F4/336 Clinical Science Center
600 Highland Avenue
Madison, WI 53792
Tel: 608-263-4823
Fax: 608-263-1466
E-mail: msip@facstaff.wisc.edu

Study Co-Chair
Ingrid U. Scott, MD, MPH
Professor of Ophthalmology and
Health Evaluation Sciences
Penn State College of Medicine
500 University Drive, HU19
Hershey, PA 17033
Tel: 717-531-5368
Fax: 717-531-5475
E-mail: iscott@psu.edu

Principal Investigator
Data Coordinating Center
Paul C. VanVeldhuisen, PhD
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850-1785
Tel: 301-251-1161 x143
Fax: 800-546-9262
E-mail: pvanveldhuisen@emmes.com

Principal Investigator
Fundus Photograph Reading Center
Barbara A. Blodi, MD
406 Science Drive, Suite 400
Madison, WI 53711
Tel: 608-263-7290
Fax: 608-263-1466
E-mail: bablodi@facstaff.wisc.edu

NEI Program Officer
Maryann Redford, DDS, MPH
National Eye Institute
6120 Executive Blvd., Suite 350
Bethesda, MD 20892
Tel: 301-451-2020
Fax: 301-402-0528
E-mail: maryann.redford@nei.nih.gov

DSMC Chair
John Connett, PhD
University of Minnesota
Coordinating Centers for Biometric Research
2221 University Avenue SE, Room 200
Minneapolis, MN 55414
Tel: 612-626-9010
Fax: 612-626-9054
E-mail: john-c@blueox.ccbr.umn.edu

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Note: A separate Manual of Policies and Procedures (MOPP) developed to accompany this protocol will provide additional details and guidance on study operational activities. A Data Management Handbook (DMH) will provide details for data collection procedures and data quality management procedures. Participating sites will be provided the necessary instructions and review of the protocol, MOPP and DMH during site visits and/or at investigator meetings. The current master protocol (incorporating any approved amendments), MOPP, and DMH are always accessible to authorized study staff via the SCORE Study web page at http://www.emmes.com/, where a username and password are required for access.

Précis

Macular edema is a major cause of vision loss in patients with central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). Currently, there is no effective treatment for macular edema associated with CRVO. For macular edema associated with BRVO, grid laser photocoagulation may be an effective treatment, but many patients derive limited benefit from this treatment. Therefore, the development of new treatment modalities to treat macular edema caused by these two conditions is an important research goal. The Standard Care vs. COrticosteroid for REtinal Vein Occlusion (SCORE) Study will compare the efficacy and safety of standard care with intravitreal injection(s) of triamcinolone acetonide to treat macular edema associated with CRVO and BRVO.

The SCORE Study is designed as a multicenter, randomized, Phase III trial to compare the efficacy and safety of standard care versus triamcinolone acetonide injection(s) for the treatment of macular edema associated with CRVO and BRVO. In each of the two disease areas, 486 participants will be randomized in a 1:1:1 ratio to one of three groups: standard care, intravitreal triamcinolone 4 mg, or intravitreal triamcinolone 1 mg. For CRVO participants, standard care consists of observation of the macular edema. For BRVO participants, standard care consists of immediate grid laser photocoagulation for study eyes without a dense macular hemorrhage. For study eyes of BRVO participants with a dense macular hemorrhage, standard care is observation followed by grid laser photocoagulation if and when clearing of the hemorrhage permits grid laser photocoagulation. For all three groups, neovascular complications will be treated as necessary. Repeat treatments will be provided as clinically indicated based on protocol-specific guidelines. Participants will be followed for between 1 and 3 years after randomization. The primary efficacy outcome of this study is improvement by 15 or more letters from baseline in best-corrected ETDRS visual acuity score at the 12-month visit. Secondary efficacy outcomes include change between baseline and each efficacy outcome assessment visit in best-corrected ETDRS visual acuity score, change in retinal thickness at the center of the macula and change in area of retinal thickening as assessed by stereoscopic color fundus photography, and change in retinal thickness and calculated retinal thickening as assessed by optical coherence tomography. Safety outcomes include injection-related adverse events such as infectious endophthalmitis,

non-infectious endophthalmitis, retinal detachment, and vitreous hemorrhage and steroid-related adverse events, which include cataract and elevated intraocular pressure.

1. Introduction

Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are common retinal vascular diseases. Macular edema from these two conditions is a frequent cause of vision loss and remains a major public health problem. Furthermore, current treatment modalities for macular edema resulting from these conditions are often unsatisfactory. At present, there is no effective treatment for macular edema from CRVO. Grid laser photocoagulation for macular edema from BRVO may, in many cases, be an effective treatment. However, many patients derive limited benefit from this treatment. A number of new treatment modalities are being developed. The majority of these is either based on complex surgical procedures or is associated with increased cost. The Standard Care vs. COrticosteroid for REtinal Vein Occlusion (SCORE) Study proposes to investigate the less expensive and relatively less invasive treatment of intravitreal injection(s) of triamcinolone acetonide for this frequent cause of visual impairment in patients with CRVO and BRVO.

The potential adverse effects of corticosteroids include cataract and elevated intraocular pressure (IOP). Delivery of corticosteroids via intravitreal injection adds potential injection-related risks of retinal detachment, vitreous hemorrhage, infectious endophthalmitis, and non-infectious endophthalmitis. As a result of these risks, further investigation is warranted to evaluate the risks of this treatment modality compared with the potential benefits. The risks associated with intravitreal injection(s) of corticosteroids may be acceptable given the opportunity to reverse vision loss from macular edema associated with CRVO or BRVO.

2. Background and Scientific Justification

2.1 Venous Occlusive Disease

CRVO and BRVO are common retinal vascular disorders. BRVO has been reported to be second only to diabetic retinopathy in the frequency with which it produces retinal vascular disease.[1] CRVO and BRVO have a characteristic appearance with intraretinal hemorrhage, tortuous and dilated retinal veins and, occasionally, optic disc edema. Macular edema is a frequent cause of visual acuity loss in eyes with CRVO and BRVO.[1-4]

In the Central Vein Occlusion Study (CVOS) 728 eyes with CRVO were studied.[2] Of these 728 eyes, 155 (21%) had macular edema that reduced visual acuity to 20/50 or worse (group M eyes, macular edema). In the largest group (group P, perfused) that included 547 eyes, 84% (460 eyes) had angiographic evidence of macular edema involving the fovea at baseline.

The natural history of macular edema associated with CRVO was delineated in the CVOS.[2-4] Additionally, the group M arm of the CVOS evaluated the treatment of macular edema with grid laser photocoagulation in 155 eyes (77 treated eyes and 78 control eyes) over a 3 year follow-up period. All eyes had macular edema for a minimum of 3 months prior to enrollment. For untreated eyes with an initial visual acuity between 20/50 and 5/200 at presentation (n=78 eyes), 42 eyes were available for follow-up at the 3-year visit. Of these eyes, 10 (24%) gained two or more lines of visual acuity at the 3-year follow-up. Twenty eyes (48%) remained within two lines of baseline visual acuity and 12 eyes (29%) lost two or more lines of visual acuity at the 3-year follow-up. At the 3-year follow-up, six eyes (14%) gained three or more lines of visual acuity. Thirty eyes (71%) remained within three lines of baseline visual acuity and six eyes (14%) lost three or more lines of visual acuity at the 3-year follow-up. The final median visual acuity in untreated eyes was 20/160.

At the 2-year visit, 53 untreated eyes were available for follow-up. Of these eyes, 10 (19%) gained two or more lines of visual acuity. Thirty-one eyes (58%) remained within two lines of baseline visual acuity and 12 eyes (23%) lost two or more lines of visual acuity at the 2-year follow-up. At the 2-year follow-up, 6 eyes (11%) gained three or more lines of visual acuity. Thirty-nine eyes (74%) remained within three lines of baseline visual acuity and eight eyes (15%) lost three or more lines of visual acuity at the 2-year follow-up.

At the 1-year visit, 72 untreated eyes were available for follow-up. Of these eyes, 6 (8%) gained two or more lines of visual acuity. Forty-four eyes (61%) remained within two lines of baseline visual acuity and 22 eyes (31%) lost two or more lines of visual acuity at the 1-year follow-up. At the 1-year follow-up, 4 eyes (6%) gained three or more lines of visual

acuity. Fifty-nine eyes (82%) remained within three lines of baseline visual acuity and nine eyes (13%) lost three or more lines of visual acuity at the 1-year follow-up.

The CVOS found no significant difference in visual outcome between the treatment and observation groups at any follow-up point. Although there was a definite decrease in macular edema on fluorescein angiography in the treatment group when compared to the control group, this did not translate to a direct visual improvement.[4] Therefore, at present, there is no proven therapy for visual impairment due to macular edema associated with CRVO. Thus, it is important to explore other avenues for managing this potentially devastating cause of vision loss.

The Branch Vein Occlusion Study (BVOS) reported on the natural history of macular edema associated with BRVO.[1] All eyes had macular edema for 3 to 18 months prior to study entry; eyes with obvious areas of capillary nonperfusion in the macula were excluded from the study. After 3 years, of 35 untreated eyes available for follow-up, only 12 eyes (34%) with a presenting visual acuity of 20/40 or worse achieved a visual acuity of 20/40 or better. Furthermore, eight eyes (23%) had 20/200 or worse visual acuity at the final 3-year follow-up visit.

The group III arm of the BVOS was designed to evaluate grid photocoagulation treatment of macular edema due to BRVO that had persisted for at least 3-months (and less than 18 months) in eyes with visual acuity of 20/40 or worse. One hundred thirty nine eyes (71 treated eyes and 68 control eyes) were studied. This arm of the study did demonstrate a benefit for eyes treated with macular grid photocoagulation.[1] Of 43 treated eyes available for follow-up at the 3-year visit, 28 eyes (65%) had gained two or more lines of visual acuity from baseline and maintained this gain for at least eight months, as compared with the same gain in 13 of 35 (37%) untreated eyes. At the 3-year visit, nearly twice as large a proportion of treated vs. control eyes had visual acuity of 20/40 or better.

Although the BVOS did demonstrate a visual acuity benefit for eyes treated with grid photocoagulation, the BVOS also identified a subset of patients that derive limited benefit

from macular grid photocoagulation. In the BVOS, 40% of treated eyes (n=43) had worse than 20/40 vision at 3 years and 12% of treated eyes had 20/200 or worse visual acuity at 3 years.[1] Therefore, for some patients with macula edema associated with BRVO current treatment options are limited and other treatment options should be sought. For example, surgical decompression of BRVO via arteriovenous crossing sheathotomy has been investigated.[5] However, this is an invasive surgical intervention with inherent risks, recovery time and expense. As a result, there is interest in exploring treatment options such as intravitreal injection(s) of triamcinolone acetonide. Table 1 summarizes visual acuity data from the two randomized clinical trials discussed above in which the natural history of macular edema from CRVO and BRVO was evaluated.

Table 1: Natural history of macular edema in two randomized trials of patients with retinal vein occlusion

Study	Vision improved by 2 or more lines		Vision unchanged (± 2 lines)		Vision worse by 2 or more lines		Number of eyes at end of study period	Follow-up period
	%	No.	%	No.	%	No.		
CVOS	24%	10	48%	20	29%	12	42	3 years
CVOS	19%	10	58%	31	23%	12	53	2 years
CVOS	8%	6	61%	44	31%	22	72	1 year
CVOS*	6%	4	82%	59	13%	9	72	1 year
BVOS	37%	13	46%	16	17%	6	35	3 years

* Improvement or worsening of vision by 3 or more lines

CVOS Central Vein Occlusion Study

BVOS Branch Vein Occlusion Study

2.2 Pathogenesis of Macular Edema

Macular edema from venous occlusive disease results from the initial insult of thrombus formation at the lamina cribrosa or an arteriovenous crossing. Green et al, in a histopathologic study of 29 eyes with CRVO, documented a fresh or recanalized thrombus of the central retinal vein in the area of the lamina cribosa as a constant pathologic finding.[6] Frangieh et al, in a histopathologic study of nine eyes with BRVO, documented a fresh or recanalized thrombus at the site of vein occlusion in all eyes studied.[7] Experimental work in

animals has demonstrated that following venous occlusion, a hypoxic environment in the retina is produced.[8] This is then followed by functional, and later structural changes, in the retinal capillaries. These changes resulted in an immediate increase in retinal capillary permeability and accompanying retinal edema.

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 vascular endothelial growth factor (VEGF), a 45 kD glycoprotein.[9] Aiello et al demonstrated in an in vivo model, that VEGF can increase vascular permeability.[9] 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 which received 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.[10] 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).[11]

The normal human retina contains little or no VEGF; however, hypoxia causes upregulation of VEGF production.[12] Disease states characterized by hypoxia-induced VEGF upregulation include CRVO and BRVO.[9,12] 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 venous

occlusive disease.[12] Pe'er et al, evaluated 10 human eyes enucleated for neovascular glaucoma from CRVO and used molecular localization with a VEGF-specific probe to identify cells producing VEGF messenger RNA (mRNA).[13] All of these eyes demonstrated upregulated VEGF mRNA expression in the retina. This hypoxia-induced upregulation of VEGF may be inhibited pharmacologically. Adamis et al demonstrated in a nonhuman primate model that anti-VEGF antibodies can inhibit VEGF driven capillary endothelial cell proliferation.[14] In this study, 16 eyes of nonhuman primates had retinal ischemia induced by laser retinal vein occlusion. Zero of eight eyes receiving neutralizing anti-VEGF antibodies developed iris neovascularization while five of eight control eyes eventually developed iris neovascularization.

As the above discussion suggests, attenuation of the effects of VEGF introduces a rationale for treatment of macular edema from venous occlusive disease. Corticosteroids, a class of substances with anti-inflammatory properties, have been demonstrated to inhibit the expression of the VEGF gene.[15] 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 inhibited by corticosteroids in a dose-dependent manner.[15] A separate study by Nauck et al demonstrated that corticosteroids downregulated the induction of VEGF by the pro-inflammatory mediators PDGF and platelet-activating factor (PAF) in a time and dose-dependent manner.[16] This study was performed using primary cultures of human pulmonary fibroblasts and pulmonary vascular smooth muscle cells.

2.3 Animal and Clinical Studies Using Intravitreal Triamcinolone Acetonide Injections

Intravitreal injection of triamcinolone acetonide has been shown to be non-toxic in animal studies.[17-19] McCuen et al injected 1mg of triamcinolone acetonide into the vitreous cavity of 21 rabbit eyes.[17] Throughout the 3-month course of follow-up ophthalmoscopy, IOP, electroretinography (scotopic and photopic responses) and light and electron microscopy all remained normal. Schindler et al studied the clearance of intravitreally injected triamcinolone acetonide (0.5 mg) in 30 rabbit eyes.[18] In non-vitrectomized eyes the average clearance rate was 41 days. In eyes having undergone vitrectomy or combination

vitrectomy and lensectomy the average clearance rate was 17 days and 7 days, respectively.[18] It was found that the ophthalmoscopic disappearance of injected triamcinolone acetonide correlated well with a spectrophotometric analysis for clearance of the drug. Scholes et al also studied the clearance of intravitreally injected triamcinolone acetonide (0.4 mg) in 24 rabbit eyes.[19] Using high-performance liquid chromatography (HPLC) complete clearance of the drug was noted by 21 days. Non-detectable drug levels (by HPLC) were present before ophthalmoscopic disappearance.

As discussed above, corticosteroids have been experimentally shown to downregulate VEGF production and possibly reduce breakdown of the blood-retinal barrier.[15,16] Similarly, steroids have antiangiogenic properties possibly due to attenuation of the effects of VEGF.[20,21] These properties of steroids are commonly utilized. Clinically, triamcinolone acetonide is used locally as a periocular injection for the treatment of cystoid macular edema (CME) secondary to uveitis or as a result of intraocular surgery.[22,23] In animal studies, intravitreal triamcinolone acetonide has been used in the prevention of proliferative vitreoretinopathy[24,25] and retinal neovascularization.[26,27] Intravitreal triamcinolone acetonide has been used clinically in the treatment of proliferative vitreoretinopathy[28] and choroidal neovascularization.[29-31]

Recently, intravitreal triamcinolone acetonide has been used clinically in the treatment of retinal vascular disease. A case report by Jonas and Sofker describes a patient with non-proliferative diabetic retinopathy with a 6-month history of persistent, diffuse macular edema despite grid photocoagulation.[32] Following one intravitreal injection of triamcinolone acetonide (20mg) 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.

Martidis et al conducted a pilot study of 16 eyes with macular edema due to diabetic retinopathy.[33,34] All 16 eyes demonstrated persistent macular edema involving the center of the macula despite each eye receiving two to six 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 five eyes were known to have macular edema for at least 6 months. All 16 eyes were treated with intravitreal triamcinolone acetonide injection and the results are summarized in Tables 2a and 2b.

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. Fourteen 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. Eight eyes completing six 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 one eye showed improvement ranging from one to five lines; nine of 14 (64%) eyes showed improvement of two or more lines at this interval. No eyes lost vision from baseline at 3-months, and all but one eye showed improvement ranging from one to five lines; nine of 14 (64%) eyes showed improvement of two or more lines at the 3-month interval. One eye lost a single line from baseline at six months and one eye remained stable; the other six eyes maintained improved visual acuity ranging from one to three Snellen lines. Four of eight (50%) eyes maintained a visual acuity improvement of two or more lines from baseline at the 6-month follow-up.

Five of 14 eyes that were evaluated at the 1-month follow-up had an IOP that exceeded 21 mmHg. The IOP in all five eyes was controlled successfully with one topical aqueous suppressant. Two of 14 eyes that were evaluated at the 3-month follow-up had an IOP that exceeded 21 mmHg. The IOP in both eyes was controlled successfully with one topical aqueous suppressant. One of eight eyes that were evaluated at the 6-month follow-up had an IOP that exceeded 21 mmHg. The IOP in this eye was controlled successfully with one

topical aqueous suppressant. The average IOP increased 45%, 20% and 13% from baseline at the 1, 3 and 6-month follow-up intervals, respectively.

Three of the eight eyes completing at least 6 months of follow-up were re-injected 6 months after initial injection due to recurrence of macular edema. 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.

Greenberg and Martidis studied both eyes of one patient with bilateral diffuse macular edema secondary to CRVO.[35] The right eye of this 80 year old patient had macular edema from a CRVO of 9 months duration when the patient presented with a 2-week history of visual acuity loss due to macular edema from a CRVO in the left eye. Because of the poor natural history of untreated macular edema in the right eye of this patient, the left eye received an intravitreal injection of triamcinolone acetonide. It did well both anatomically and functionally, with visual acuity improvement from 20/400 to 20/30 after three months of follow-up. Central foveal thickness as measured by optical coherence tomography decreased from 589 microns to 160 microns with restoration of a normal foveal contour following treatment. Six months following injection, visual acuity decreased to 20/400 because of recurrence of retinal thickening that measured 834 microns by optical coherence tomography. A second injection was performed and, 1 month later, visual acuity returned to 20/50 with a decrease in central foveal thickness to 158 microns with a normal foveal contour. This patient has maintained this level of visual acuity for over 6 months following the second injection. Given the response to treatment in the left eye, the right eye (now with 16 months of untreated macular edema) was treated with an intravitreal injection of triamcinolone acetonide. There was a prompt reduction in central foveal thickness as measured by optical coherence tomography from 735 microns to 195 microns. However, possibly as a result of the duration of macular edema, no visual benefit was noted. No significant elevation of IOP was noted in either eye.

Other clinical case reports by Ip et al and Jonas et al have demonstrated similar results in the treatment of macular edema due to CRVO with intravitreal injections of triamcinolone

acetonide.[36,37] Recently, Park et al evaluated intravitreal triamcinolone injection(s) as a treatment of macular edema associated with CRVO.[38] Ten eyes of 9 patients with perfused CRVO with visual acuity 20/50 or worse were treated with an intravitreal injection of triamcinolone acetonide (4mg/0.1cc). One patient received a repeat injection. The mean duration from time of diagnosis to the intravitreal triamcinolone injection was 15.4 months. The mean best-corrected visual acuity improved from 58 letters (range, 37-72) at baseline to 78 letters (range 50-100 letters) at last follow-up (mean, 4.8 months). Volumetric optical coherence tomography (VOCT) was performed on 9 of 10 patients at baseline and follow-up. VOCT measurements improved from a mean of 4.2 mm^3 at baseline to a mean of 2.6 mm^3 at last follow-up (normal range of VOCT is 2.0-2.5 mm^3). Three eyes without a previous history of glaucoma required topical antiglaucoma medication. One eye with a previous history of open-angle glaucoma required trabeculectomy surgery.

Table 3 lists the frequency and nature of adverse effects seen in some of the largest clinical studies thus far using intravitreal triamcinolone acetonide. Penfold and Challa studied 30 eyes with exudative macular degeneration.[29,30] No adverse events such as retinal detachment, vitreous hemorrhage or endophthalmitis were noted. However, three of four eyes that received a second injection of triamcinolone acetonide experienced rapid progression of cataract within 2 months of re-injection. Two of these four eyes also experienced steroid-induced glaucoma with IOP elevation to 37 mmHg. Both eyes had argon laser trabeculoplasty and were treated with topical aqueous suppressants. One of these two eyes required trabeculectomy surgery to control IOP. In another series, Danis et al injected 16 eyes with exudative macular degeneration.[31] No adverse events such as retinal detachment, vitreous hemorrhage or endophthalmitis were noted. Four of seven phakic patients developed progressive lens opacities that over the 6-month follow-up did not require cataract surgery. Four patients developed transient IOP 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 IOP over 32 mmHg at any point in follow-up.

The other studies listed in Table 3 all demonstrate a similar adverse event profile.[28,39-41] A summary of the data from the seven studies listed shows that the frequency of injection-related adverse events such as endophthalmitis, non-infectious endophthalmitis, retinal detachment and vitreous hemorrhage appear rare based on these small studies in the published literature. Corticosteroid-related adverse events, from the data in Table 3, are more common. However, corticosteroid-related adverse events (cataract and elevated IOP) appear to be manageable. For example, of the 221 patients in the seven studies discussed, 33 patients (15%) were noted to have some elevation of IOP; all patients were managed successfully with topical aqueous suppressants except one patient who required argon laser trabeculoplasty and one patient who required both argon laser trabeculoplasty and trabeculectomy. Nine patients (4%) required cataract surgery and 24 patients (12%) were noted to have progressive lens opacity.

Table 2a: Clinical characteristics of sixteen patients treated with intravitreal triamcinolone injection for diabetic macular edema not responsive to focal/grid photocoagulation

Case	Eye	Age	Lens	Retinopathy	Duration ME (mo)	Prior Laser
1	OS	72	Pseudo	NPDR	21	2
2	OD	48	Phakic	PDR	36	2
3	OS	85	Phakic	NPDR	29	3
4	OS	76	Phakic	NPDR	13	2
5	OS	70	Pseudo	NPDR	23	3
6	OD	68	Phakic	NPDR	47	5
7	OD	70	Phakic	PDR	>6	2
8	OD	59	Phakic	NPDR	>6	2
9	OS	67	Phakic	NPDR	26	2
10	OD	52	Phakic	PDR	68	3
11	OS	71	Pseudo	NPDR	50	6
12	OS	74	Phakic	NPDR	12	2
13	OS	62	Phakic	NPDR	>6	2
14	OS	65	Phakic	NPDR	24	2
15	OD	43	Phakic	NPDR	>6	2
16	OD	62	Phakic	NPDR	>6	2

Table 2b: Clinical characteristics of sixteen patients treated with intravitreal triamcinolone injection for diabetic macular edema not responsive to focal/grid photocoagulation

Visual Acuity				OCT (microns)				IOP (mmHg)				F/U	Reinject
Initial	1 mo	3 mo	6 mo	Initial	1 mo	3 mo	6 mo	Initial	1 mo	3 mo	6 mo	(mo)	(mo)
20/400	20/200	20/200	20/200	612	378	214	236	14	24	18	16	12	No
20/80	20/50	20/60	20/100	569	171	132	519	16	20	18	16	11	11
20/200	20/60	20/60	20/60	550	177	181	208	18	12	14	20	11	No
20/400	20/200	20/100	20/100	401	232	199	174	17	22	33	16	10	No
20/400	20/200		20/400	557	154		621	15	28		14	9	6
20/200		20/80	20/100	583		109	90	15		17	23	8	No
20/400	20/60		20/100	703	264		588	14	21		16	7	6
20/60	20/30	20/30	20/40	348	268	270	242	10	17	13	13	6	No
20/800	20/100	20/100		564	397	360		17	17	22		5	No
20/80	20/60	20/60		585	199	188		15	18	15		4	No
20/200	20/200	20/100		510	260	265		12	17	11		3	No
20/400		20/400		596		233		14		14		3	No
20/200	20/60	20/40		497	213	180		12	30	16		3	No
20/200	20/60	20/60		497	239	424		15	16	20		3	No
20/200	20/40	20/40	20/40	674	262	204		17	20	16		3	No
20/100	20/50	20/40		399	180	176		14	36	20		3	No

NPDR: non-proliferative diabetic retinopathy
PDR: proliferative diabetic retinopathy
ME: macular edema
Pseudo: pseudophakic
OCT: optical coherence tomography
IOP: intraocular pressure

Table 3: Summary of adverse events from seven case series using intravitreal triamcinolone acetonide

	# Eyes treated	Disease	Dose (mg)	IOP rise	Cataract (surgery)	Lens Opacity	R.D.	Vit Heme	Endophth	Non-infectious endophthalmitis
Wingate[39]	113	AMD	4	12	NA	NA	NA	NA	NA	NA
Penfold[29]	30	AMD	4	3	9	1	0	0	0	0
Danis[31]	16	AMD	4	4	0	4/7 phakic	0	0	0	0
Jonas[28]	16	PVR	10-20	0	0	0	0	0	0	1
Martidis[33]	16	DME	4	5	0	1	0	0	0	0
Jonas[40]	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

AMD Age-related macular degeneration
DME Diabetic macular edema
PVR Proliferative vitreoretinopathy
NVG Neovascular glaucoma
RD Retinal detachment
NA Not available; these adverse events were not specifically discussed in the manuscript

2.4 Other Studies Evaluating Corticosteroid Preparations Other Than Triamcinolone Acetonide for Treatment of Macular Edema due to Retinal Vascular Disease

2.4.1 Efficacy

2.4.1.1 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 of the eye 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 was between 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: 0.5 mg implant (N=41), 2 mg implant (N=11) or standard of care treatment consisting of either repeat laser photocoagulation or observation (N=28). (The 6-month data shown 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 0.5 mg 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 two or more step decrease in retinal thickening at the center of the fovea was greater in eyes that received the 0.5 mg implant than those assigned to standard of care treatment ($P=0.026$). This result remained statistically significant at the 12-month follow-up ($P=0.003$).

2.4.1.2 Oculex

Oculex is developing a biodegradable, implantable, extended release product (Posurdex) that delivers the corticosteroid dexamethasone directly to the posterior segment of the eye for a period of 35 days. A phase two clinical trial was completed evaluating two 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 two or more lines on the ETDRS chart when compared to patients who did not receive the implant (P=0.019).
- Secondary outcomes such as retinal thickness and fluorescein leakage also showed statistically significant decreases in patients that received the 700 microgram implant when compared to 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.

2.4.2 Adverse Effects

2.4.2.1 Control Delivery Systems (Bausch and Lomb)

Elevated IOP

- At the 6-month follow-up, 12.2% of patients in the 0.5 mg implant group had an IOP elevation to 30 mmHg or more. All patients were

managed with topical antiglaucoma medication. No eye in the standard of care group had such an elevation in IOP.

- At the 12-month follow-up, 19.5% of patients in the 0.5 mg implant group had an IOP elevation that was considered a serious adverse event. Three patients in the 0.5 mg implant group required trabeculectomy surgery. No eye in the standard of care group had such an elevation in IOP.

Cataract

- At the 6-month follow-up, 0.0% of patients in the standard of care group had "cataract progression". Seventeen percent of patients in the 0.5 mg group had "cataract progression.
- At the 12-month follow-up, 0.0% of patients in the standard care group had cataract progression defined as a serious adverse event. Forty-one percent of patients in the 0.5 mg group (all study eyes) had cataract progression defined as a serious adverse event.

2.4.2.2 Oculex

Elevated IOP

- An IOP elevation to 25 mmHg or more was noted at some point in the study in 32 eyes; all were readily controlled with topical antiglaucoma medication.

Cataract and other side effects

- There was no difference in cataract progression between the study groups.
- No other safety concerns were noted.

2.5 Rationale for the Intravitreal Triamcinolone Acetonide Doses to be Evaluated

The optimal dose of triamcinolone acetonide to maximize efficacy with minimum side effects is not known. A 4 mg dose of Kenalog, a commercially available preparation that is FDA labeled for intramuscular or intrabursal use, 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 1 mg and 2 mg. These doses anectodally have been reported to reduce macular edema. There is a rationale for using a dose lower than 4 mg.[42,43] 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 at about 20 fold higher levels, so about 100 nanomolar. A 4 mg dose of triamcinolone/4mg of vitreous volume yields a final concentration of 7.5 millimolar, or nearly 10,000 fold more than the saturation dose. Thus, the effect of a 1 mg 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 0.5 mg 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 4 mg. Jonas' case series described earlier reported results using both a 20mg and 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 SCORE Study, 4 mg and 1 mg doses will be evaluated. The former 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 1 mg dose will reduce macular edema, it is possible that the retreatment rate will be higher with this dose compared with 4 mg 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.

2.6 Mechanism of Adverse Effects Associated with Intravitreal Steroids

2.6.1 Elevation of Intraocular Pressure

IOP depends on the comparative rates of aqueous production and aqueous drainage, primarily through the trabecular meshwork. Increased IOP 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 IOP may result in glaucomatous optic nerve changes and loss of visual field.

Among the secondary open-angle glaucomas, corticosteroid-induced elevation of IOP is one of the most common. This relationship is well established. In patients susceptible to this phenomenon, the elevation of IOP may occur as a result of topical, systemic or peribulbar administration. For example, following 4-6 weeks of topical corticosteroid administration, 5% of subjects may show an elevation in IOP of >16mmHg and 30% of subjects may show an elevation of 6-15mmHg.[44,45]

The mechanism of corticosteroid induced elevation of IOP is incompletely understood. Possible theories include[46]: 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, f) stabilization of lysosomes which allow accumulation of hyaluronate or other debris in the trabecular meshwork.

The intravitreal administration of corticosteroid is expected to be associated with an increase in IOP in susceptible patients. Indeed, the literature reviewed in this protocol confirm that corticosteroid induced elevation in IOP may result from intravitreal corticosteroid administration (Table 3). The time course for the development of corticosteroid induced elevation in IOP as a result of intravitreal injection is presently

unknown. Additionally, the effect of the initial dose administered, the frequency of reinjection or the cumulative dose administered over time on the severity of IOP elevation is not known. The experience thus far indicates that the 4 mg and 25 mg doses of triamcinolone acetonide appear to result in a relatively similar frequency and severity of IOP elevation [33,41] Reinjection of the 4 mg dose at a frequency of more than once every four months appears to be associated with more frequent and more severe elevation in IOP.[29]

All patients who receive intravitreal injection of corticosteroid will have IOP monitored carefully in this study. The frequency and severity of IOP elevation will be monitored.

2.6.2 Cataract Formation

An opacity of the lens that results in loss of transparency and/or causes light scatter is called a cataract. The reasons why cataracts occur 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.[47] 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. Topical, systemic and

peribulbar corticosteroid administration have all been associated with an increased risk of cataract formation.[48] Even the prolonged administration of inhaled corticosteroids has been associated with an increased risk of cataract formation.[49]

The intravitreal administration of corticosteroid is also expected to be associated with cataract formation. Indeed, the literature reviewed in this protocol confirms that cataracts appear to result from intravitreal corticosteroid administration (Table 3). 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 1 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. Table 3 shows that 4% of patients in the 7 pooled studies required cataract surgery and 12% had progressive lens opacity. These studies had at least 3 months of follow-up and, in some cases, substantially more.

Corticosteroid induced cataract will be followed closely as an adverse event in this study.

2.6.3 Endophthalmitis

Infectious endophthalmitis is an intraocular inflammatory process due to infection with pathogens such as bacteria or fungi. Clinical features include lid edema, conjunctival injection, corneal edema, anterior chamber and vitreous inflammation, and hypopyon. Infectious endophthalmitis can occur following an intraocular procedure (e.g. cataract surgery, vitrectomy surgery, intravitreal injection), as a result of systemic infection, as a result of trauma, or occur as a late feature of conjunctival filtering blebs.

Acute postoperative 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%.[50] In the Endophthalmitis Vitrectomy Study (EVS), gram-positive organisms accounted for 94% of culture positive cases.[51]

The incidence and causative pathogens following intravitreal injection of corticosteroid are less well defined. In the published literature, this complication appears uncommon (Table 3). Endophthalmitis following 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 that has immunosuppressive properties may result in a higher incidence of postinjection endophthalmitis using corticosteroids. A standardized protocol to prepare eyes for the injection procedure may help to decrease the incidence of this complication. Such a protocol is described in the Manual of Procedures and Procedures (MOPP).

The clinical experience 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.[52] Although the published literature to date does not describe a significant incidence of complications as a result of the Kenalog vehicle, anecdotal experience suggests that there may be a significant incidence of non-infectious endophthalmitis as a result of the vehicle components [American Society of Retinal Specialists listserve from 2002-2003]. As a result of the possibility of a sterile reaction to the components of the Kenalog vehicle, it is difficult to be certain if an inflammatory reaction is infectious or non-infectious following an injection of Kenalog. Treatment of infectious endophthalmitis requires immediate treatment with intravitreal antibiotics with or without vitrectomy surgery depending on the clinical situation. Non-infectious endophthalmitis is usually self-limiting. A sterile, preservative-free triamcinolone preparation will be used in this study.

Despite the use of a sterile, preservative-free preparation, inflammatory reactions following intravitreal injection as well as the frequency of infectious endophthalmitis will be monitored carefully in this study.

3. Objectives

The primary objective of the SCORE Study is to compare visual acuity outcome among 3 groups of participants: those who are randomly assigned to receive standard care and those randomly assigned to receive one of two doses of intravitreal injection(s) of triamcinolone acetonide for treatment of macular edema associated with CRVO and BRVO. Secondary objectives include estimating the incidence of infectious endophthalmitis, non-infectious endophthalmitis, retinal detachment, vitreous hemorrhage, cataract and elevated IOP in eyes receiving intravitreal injection(s) of triamcinolone. Other secondary objectives include comparing changes in retinal thickness and calculated retinal thickening in participants who are randomly assigned to receive intravitreal injection(s) of triamcinolone acetonide with those randomly assigned to standard care for treatment of macular edema associated with CRVO and BRVO.

4. Study Design and Methods

The SCORE Study is a multicenter, randomized, Phase III trial designed to compare the efficacy and safety of standard care with intravitreal injection(s) of triamcinolone acetonide for the treatment of macular edema associated with CRVO and BRVO. Eligible participants within each of these two disease entities will be randomized in a 1:1:1 ratio to one of three groups (treatment of neovascular complications as necessary in all three groups):

1. Standard care group: conventional treatment consisting of:
    a. CRVO:
        i. Observation of macular edema.
    b. BRVO:
        i. Study eyes with dense macular hemorrhage: Immediate observation. Grid laser photocoagulation will be performed if and when clearance of hemorrhage permits grid laser photocoagulation.

ii. Study eyes without dense macular hemorrhage: Immediate grid laser photocoagulation.

or

2. Intravitreal injection(s) of 4 mg of triamcinolone acetonide,

or

3. Intravitreal injection(s) of 1 mg of triamcinolone acetonide.

Note: Patients and investigators will be masked to the triamcinolone acetonide dose used (1 mg or 4 mg).

4.1 Efficacy Assessment

4.1.1 Primary Efficacy Outcome

The primary efficacy outcome of this study is improvement by 15 or more letters from baseline in best-corrected ETDRS visual acuity score at the 12-month visit as determined by the ETDRS visual acuity protocol. The primary outcome analysis will include the following three comparisons of the proportion of participants having a 15 ETDRS letter improvement from baseline to 1 year:

- 4 mg triamcinolone acetonide intravitreal injections with standard care
- 1 mg triamcinolone acetonide intravitreal injections with standard care
- 4 mg triamcinolone acetonide intravitreal injections with 1 mg triamcinolone acetonide intravitreal injections

4.1.2 Secondary Efficacy Outcomes

Secondary efficacy outcomes include the following:

- Change between baseline and each efficacy outcome assessment visit in best-corrected ETDRS visual acuity score (e.g., mean change from baseline in visual acuity, distribution of change from baseline in visual acuity based on clinically meaningful cut points of improvement or worsening of visual acuity).

- Change in calculated retinal thickening as assessed by optical coherence tomography.
- Change in retinal thickness at the center of the macula as assessed by stereoscopic color fundus photography.
- Change in area of retinal thickening as assessed by stereoscopic color fundus photography.

4.2 Safety Assessments

4.2.1 Safety Outcomes

Safety outcomes will be tabulated by observing the nature, severity and frequency of adverse events throughout the three years of the study. Specific safety outcomes include:

- Injection-related events including infectious endophthalmitis, non-infectious endophthalmitis, retinal tear or detachment, vitreous hemorrhage, ocular discomfort/irritation, ocular tenderness, ocular itching sensation, foreign body sensation, blurred vision, floaters, corneal abrasion, subconjunctival hemorrhage, conjunctival edema, and conjunctival hyperemia/erythema.
- Steroid-related toxicities including cataract and elevated IOP.

4.3 Inclusion Criteria

4.3.1 General Inclusion Criteria

a. Ability and willingness to provide informed consent.

b. Sex: Participants may be male or female.

c. Age: 18 years or older

4.3.2 Ocular Inclusion Criteria (study eye)

a. Participants must have center-involved macular edema secondary to either CRVO or BRVO. Eyes may be enrolled as early as the time diagnosis of the macular edema, but not longer than 24 months after

diagnosis (by patient history or ophthalmologic diagnosis). The following definitions are used for the purposes of the SCORE Study:

i. A CRVO is defined as an eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g. telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in all 4 quadrants.

ii. A BRVO is defined as an eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g. telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in 1 quadrant or less of retina drained by the affected vein.

iii. A hemiretinal vein occlusion (HRVO) is defined as an eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g. telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in more than 1 quadrant but less than all 4 quadrants. Typically, a HRVO is a retinal vein occlusion that involves 2 altitudinal quadrants. *For the purposes of the SCORE Study, eyes with HRVO will be treated as eyes with BRVO and analyzed with the BRVO group.*

b. ETDRS visual acuity score of greater than or equal to 19 letters (approximately 20/400) and less than or equal to 73 letters (approximately 20/40) by the ETDRS visual acuity protocol.

- Note: There will be an enrollment limit of 15% of eyes with visual acuity between 19 and 33 letters. The investigator must believe that a study eye with visual acuity between 19 and 33 letters is perfused.

c. Mean retinal thickness on two OCT measurements greater than or equal to 250 microns (central subfield).

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

4.4 Exclusion Criteria

4.4.1 General Exclusion Criteria

Participants with any of the following conditions are ineligible:

a. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., chronic alcoholism or drug abuse, personality disorder or use of major tranquilizers indicating difficulty in long term follow-up, likelihood of survival of less than 3 years).

b. Participation in an investigational trial within 30 days of study entry that involved treatment with any drug that has not received regulatory approval at time of study entry.

c. History of allergy to any corticosteroid or component of the delivery vehicle.

d. Sitting systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 110 mmHg. If the initial reading exceeds these values, a second reading may be taken two or more hours later; the patient may be included (if all other inclusion criteria are met) in the study if the second reading demonstrates a systolic blood pressure equal to or less than 180 mmHg and the diastolic blood pressure is 110 mmHg or less. If the blood pressure is brought to 180 mmHg systolic or less and 110 mmHg diastolic or less by antihypertensive treatment, the patient can become eligible.

e. The participant will be moving out of the area of the clinical center to an area not covered by another clinical center during the 3 years of the study.

f. History of systemic (e.g., oral, IV, IM, epidural, bursal) corticosteroids within 4 months prior to randomization or corticosteroid eyedrops in current use more than 2 times per week.

- Note: Patients taking topical, rectal or inhaled corticosteroids are eligible for the study.

g. Positive urine pregnancy test: all women of childbearing potential (those who are pre-menopausal and not surgically sterilized) may participate only if they have a negative urine pregnancy test, if they do not intend to

become pregnant during the timeframe of the study and if they agree to use at least one of the following birth control methods: hormonal therapy such as oral, implantable or injectable chemical contraceptives; mechanical therapy such as spermicide in conjunction with a barrier such as a condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner.

4.4.2 Ocular Exclusion Criteria (study eye)

a. Exam evidence of vitreoretinal interface disease (e.g. vitreomacular traction, epiretinal membrane), either on clinical examination or optical coherence tomography thought to be contributing to macular edema.
b. An eye that, in the investigator's opinion, would not benefit from resolution of macular edema such as eyes with foveal atrophy, dense pigmentary changes or dense subfoveal hard exudates.
c. Presence of an ocular condition that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., age-related macular degeneration, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, prior macula-off rhegmatogenous retinal detachment).
d. Presence of a substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (i.e. a 20/40 cataract).
e. History of laser photocoagulation for macular edema within 4 months prior to randomization.
    - Note: If prior grid laser photocoagulation has been performed, the study eye must have either:
        a. One or more disc areas of leakage on the fluorescein angiogram (FA). This area of leakage must be contiguous with the fovea and have no evidence of prior laser treatment.

OR

b. Two or more disc areas of leakage on the fluorescein angiogram (FA). This area of leakage must be contiguous with the fovea and have evidence of clearly inadequate prior laser treatment.

f. History of intravitreal corticosteroid injection.

g. History of peribulbar or retrobulbar corticosteroid use for any reason within 6 months prior to randomization.

h. History of panretinal scatter photocoagulation (PRP) or sector laser photocoagulation within four months prior to randomization or anticipated within the next four months following randomization.

i. History of pars plana vitrectomy.

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

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

l. IOP greater than or equal to 25 mm Hg.

m. Exam evidence of pseudoexfoliation.

n. History of steroid-induced IOP elevation that required IOP-lowering treatment.

o. History of open angle glaucoma (either primary open angle glaucoma or other cause of open angle glaucoma; note: prior angle closure glaucoma is not an exclusion).

- A history of ocular hypertension (or IOP greater than or equal to 22 mm Hg without a prior diagnosis of ocular hypertension) is not an exclusion as long as (1) IOP is less than 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 macular disease), and (4) the optic nerve does not appear glaucomatous.

- Note: If IOP is 22 to less than 25 mm Hg, then the above criteria for ocular hypertension eligibility must be met.

p. History of herpetic ocular infection.

q. History of ocular toxoplasmosis.

r. Aphakia.

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

t. History of macular detachment.

u. Exam evidence of any diabetic retinopathy, defined as eyes of diabetic patients with more than one microaneurysm outside the area of the vein occlusion (inclusive of both eyes).

v. History of idiopathic central serous chorioretinopathy.

4.4.3 Fellow (Non-Study) Eye Criteria (the Fellow Eye Must Meet the Following)

a. ETDRS visual acuity score of greater than or equal to 19 letters (approximately 20/400)

b. No prior history of intravitreal corticosteroid injection.

c. IOP less than 25 mm Hg.

d. No exam evidence of pseudoexfoliation.

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

f. 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 (or IOP greater than or equal to 22 mm Hg without a prior diagnosis of ocular hypertension) is not an exclusion as long as (1) IOP is less than 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 macular disease), and (4) the optic nerve does not appear glaucomatous.

- Note: If the IOP is 22 to less than 25 mm Hg, then the above criteria for ocular hypertension must be met

4.5 Informed Consent, Screening Evaluation, and Randomization

4.5.1 Informed Consent

Potential participants in the SCORE Study will be assessed as part of routine-care examinations. Prior to completing any procedures or collecting any data that are not part of usual medical care, written informed consent will be obtained. The informed consent should be reviewed with the patient at this visit and signed with the understanding that the patient may or may not be eligible. Consent may be given in two stages (if approved by the IRB), with one consent signature obtained prior to screening procedures specific to the SCORE Study that are needed to assess eligibility. The second stage will be obtained prior to randomization and will be for participation in the SCORE Study. Thus, a single consent form will have two signature/date lines for the patient: one for the patient to consent to the screening procedures and one for the patient to consent for the randomized trial. Patients will be encouraged to discuss the SCORE Study with family members and their personal physician(s) before deciding on study participation. Two identical consent forms are signed. One original consent form is to be kept in the participant's study file and a copy of an original is placed in the participant's clinical chart. The other original signed consent is for the participant to take home. The informed consent describes the study, randomization procedure, intravitreal steroid treatment and participant responsibilities. Randomization will occur following confirmation of the patient's eligibility for the study and decision to enter the study.

4.5.2 Screening Evaluation

a. An interview is conducted, including demographic information, medical history including ocular history and current medications. This history is taken in order to ascertain whether there is any medical, ocular, or medication condition that may indicate ineligibility. *Participants who are*

taking aspirin or warfarin are eligible for the study. However, participants may be requested to refrain from taking warfarin a few days prior to the randomization visit and/or any retreatment visits if they are assigned to receive corticosteroid treatment; this decision is at the discretion of the investigator and the patient's primary care physician.

b. Visual acuity and manifest refraction *(done within 8 days prior to randomization)*. Visual acuity testing and manifest refraction are done using electronic ETDRS (E-ETDRS) visual acuity testing at 3 meters using the Electronic Visual Acuity Tester by a SCORE certified technician. This testing procedure has been validated against 4 meter standard ETDRS chart testing. Given the critical importance of visual acuity in this study, the best-corrected E-ETDRS visual acuity must be obtained in this very careful and standardized manner. *Additionally, a "masked" visual acuity examiner with no knowledge of treatment assignments will perform visual acuity testing at the 4-month, 12-month, 24-month and 36-month visits. This "masked" examiner will be an individual not involved with the study except for the purpose of performing visual acuity testing. For example, this individual may be a clinic technician or a study coordinator for another clinical trial, but may not be the study coordinator for this trial.*

c. IOP *(done within 21 days prior to randomization)*. The IOP of both eyes will be measured prior to randomization. IOP will be measured using a sterile Goldmann applanation tonometer (see MOPP for procedure details).

d. Ophthalmic examination including dilated ophthalmoscopy *(done within 21 days prior to randomization)*. The participant's ocular status is evaluated by a study participating ophthalmologist for conditions that may make the participant ineligible as well as information necessary to complete the study forms. Lens assessment for cataract at the slit lamp will be performed with grading according to a modified Age-Related Eye Disease Study (AREDS) grading system.

e. Fundus photographs, fluorescein angiography and optical coherence tomography *(done within 21 days prior to randomization)*. Good quality stereoscopic color fundus photographs (7 fields of the study eye and 3 fields of the fellow eye) and a fluorescein angiogram as well as two optical coherence tomography measurements per eye are required for all participants. The mean of the 2 OCT measurements will be used to assess eligibility. These procedures are described in: University of Wisconsin-Madison Fundus Photograph Reading Center Fluorescein Angiography and Optical Coherence Tomography protocols.

f. Blood pressure measurement *(done within 21 days prior to randomization)*.

g. For women of childbearing potential: Urine pregnancy test *(done within 21 days prior to randomization)*.

4.5.3 Randomization

A secure Internet-based eligibility, enrollment and randomization system is integrated into the SCORE Study. One eye of each participant will be randomly assigned to either treatment with intravitreal triamcinolone acetonide in one of two doses (4 mg or 1 mg) vs. observation (CRVO) or intravitreal triamcinolone acetonide in one of two doses (4 mg or 1 mg) vs. observation/grid laser photocoagulation (BRVO). Treatment assignments, generated by the SCORE Data Coordinating Center, will be stratified according to the following disease groups: CRVO, BRVO without dense macular hemorrhage, and BRVO with dense macular hemorrhage; and baseline visual acuity according to the following categories: good visual acuity (59-73 letters: 20/40 to 20/63), moderate visual acuity (49-58 letters: 20/80 to 20/100), and poor visual acuity (19-48 letters: 20/125-20/400). In participants with both eyes eligible and when both eyes have the same disease (CRVO or BRVO), the eye to be randomized into the SCORE Study will be at the discretion of the physician and patient. Only one eye per participant may be randomized into the SCORE study. In participants with both eyes eligible, but where the disease is different (i.e. CRVO in one eye and

BRVO in the other eye) the eye to be randomized into the SCORE Study will also be at the discretion of the physician and patient.

4.6 Standard Care Groups

For study eyes with CRVO, standard care consists of observation of the macular edema. For study eyes of BRVO participants with a dense macular hemorrhage, standard care is observation followed by grid laser photocoagulation if and when clearing of the hemorrhage permits grid laser photocoagulation. For study eyes of BRVO participants without a dense macular hemorrhage at enrollment, standard care consists of immediate grid laser photocoagulation. The determination of a dense hemorrhage in the center of the macula (and thus the timing of the grid laser photocoagulation) is left to the discretion of the investigator. For all three groups, neovascular complications will be treated as necessary.

The timing of, and criteria for, retreatment with laser photocoagulation are detailed in Section 4.8.3.

4.6.1 Photocoagulation Procedures

Participants with BRVO assigned to standard care who are eligible for laser (i.e., no dense macular hemorrhage) will have laser photocoagulation performed to treat both focal leaks, if any, and areas of diffuse retinal thickening. The investigator has the flexibility to determine the total number of burns required for treatment. However, the total number of burns delivered will depend on the number of focal leaks present, if any, and the area of diffuse retinal thickening present. If the eye is not eligible for laser photocoagulation at the randomization visit because of the presence of dense macular hemorrhage, the participant will be re-evaluated at 4-month intervals. If the macular hemorrhage clears, laser photocoagulation will be performed at that time. The following guidelines should be followed:

Grid Laser Photocoagulation Procedure

Size	50-100 um
Exposure	0.05-0.1 seconds
Intensity	Mild
Number	Cover areas of diffuse retinal thickening and treat focal leaks if any are present
Placement	1-2 burn width apart (500-3000um from center of fovea)
Wavelength	Green to yellow

4.7 Intravitreal Steroid Groups

Study eyes of CRVO and BRVO participants randomized to intravitreal steroid injection(s) will be given triamcinolone acetonide, in a masked fashion, in one of two doses (1 mg or 4 mg), depending on the treatment assignment.

The timing of, and criteria for, retreatment with intravitreal triamcinolone injections are detailed in section 4.8.3.

4.7.1 Intravitreal Injection of Triamcinolone Acetonide

The study drug formulation (triamcinolone acetonide) used in the SCORE Study has been developed by Allergan, Inc. (Irvine, CA). The physical, chemical and pharmaceutical properties of the study drug and formulation are detailed in the Clinical Investigator's Brochure. Topical antibiotic drops will be administered in the study eye prior to injection (on the day of injection) and for three days post injection. Prior to injection, a standard prep will include povidone iodine and a sterile lid speculum. The same technique is followed for both the initial treatment and for retreatment. The full injection procedure is described in the SCORE Study MOPP.

4.8 Participant Visit Schedule, Retreatment, Alternate Treatment and Other Treatments

Note: The SCORE Study protocol under protocol versions 6.0 and earlier specified 3 year follow-up on all study participants. Under Protocol version 7.0 and higher (February 10, 2008), the last day of enrollment is February 29, 2008 and the last day of participant follow-up is February 28, 2009 to allow all participants at least one year of follow-up for primary efficacy assessment. Testing procedures at a study participant's final study visit, which will take place at one of the following visits: M12, M16, M20, M24, M28, M32, or M36, will be performed as described in Section 4.8.2. Patients who are injected in February 2009 will still need to come in for their Day 4 and Month 1 safety visits, even though these safety visits may be late, i.e. they may occur after February 28, 2009. (Late safety visits are required to safeguard patient safety, but, to ensure comparability between groups, late safety visits will not be part of the trial safety analysis). All study participants active under Protocol Version 7.0 who will not reach their Month 36 visit by February 28, 2009 will be asked to sign an addendum to the informed consent form.

4.8.1 Visit Schedule

Appendix 1 shows the follow-up visit schedule for all participants through month 36. Participants in each of the 3 treatment groups will have follow-up visits every 4 months. The visit windows are ± 2 weeks during the first 12 months and ± 8 weeks after 12 months.

- The visits at 4 months (± 2 weeks), 12 months (± 2 weeks), 24 months (± 8 weeks), and 36 months (± 8 weeks) are designated for outcome assessment visits. At these visits, certain additional testing is performed that is not performed at other visits.
- 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 study participant

- In the intravitreal triamcinolone groups, post-injection safety visits will be performed at 4 days and 4 weeks after each intravitreal injection.

- Assessment of ocular symptoms or ocular problems other than for macular edema or the follow-up of adverse events may require additional visits. These visits are to be scheduled promptly at the investigator's discretion.

4.8.2 Testing Procedures to be Performed at Follow-up Visits (see Appendix 1)

The following procedures will be performed at each 4-month follow-up visit on both eyes unless otherwise specified.

1. E-ETDRS visual acuity. Protocol refraction will be performed at the 4, 12, 24 and 36 month visits. At other visits, the need for a refraction is determined by the investigator based on usual care considerations. A refraction should be performed when there is a change in visual acuity of 15 or more letters (better or worse) from the visual acuity score at the time of the last refraction.
2. IOP measurement using the Goldmann tonometer.
3. Ophthalmic examination, including a dilated fundus examination and a slit-lamp examination.
4. Fundus photography. Three field fundus photography will be performed on the study eye at all visits except at 12, 24, and 36 months, at which time seven field fundus photography will be performed. Three field fundus photography will be performed on the non-study eye at 12, 24, and 36 months.
5. Optical coherence tomography. To be performed on both eyes at 4, 12, 24, and 36 months and on the study eye only at other visits.
6. Lens assessment, using modified AREDS standard lens photographs, for cataract will be performed at 4, 12, 24, and 36 months.
7. Fluorescein angiography will be performed at 4, 12, and 24 months. The fluorescein angiography protocol directs image capture from both eyes, with emphasis on the study eye.
8. Blood pressure measurements will be performed at 12, 24, and 36 months.

Visual acuity, IOP, and an ophthalmic examination will be performed at the 4-day (+/-3 days) and 4-week (+/-7 days) post-injection safety visits. At unscheduled visits, the procedures performed will be determined by the investigator.

4.8.3 Retreatment Assessment

At each 4-month visit during follow-up, the investigator will assess whether persistent or recurrent macular edema is present that warrants retreatment with the randomization assigned treatment.

Only those eyes assigned to intravitreal triamcinolone and those eyes eligible for laser photocoagulation (i.e. eyes with BRVO and without a dense macular hemorrhage) are eligible for retreatment.

Retreatment, when indicated, will be performed within 4 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, then the patient can either be scheduled to be seen in 4 months or can be seen sooner at investigator's discretion.

4.8.3.1 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 not be considered flat if the OCT central subfield is greater than 225 microns).*
b. ETDRS visual acuity score of 79 or more letters (approximately 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 thickening [thickening is not retinal thickness; it is the difference between normal retinal thickness and observed retinal thickness] in the central subfield) AND 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 participant had an IOP elevation after a previous steroid injection that required treatment to lower the IOP. (*Note: an investigator may choose to retreat a participant who developed IOP elevation that has been controlled or is currently controlled with treatment as long as IOP currently is 35 mm Hg or less. If the IOP is greater than 35 mm Hg, 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 seems "apparently futile":
   Additional treatment will be defined as "apparently futile" if 8 or more months transpire, during which there have been 2 procedures (either laser

photocoagulation 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 the 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 (measured thickness minus 175 microns) compared with the findings at the beginning of the 8 or more months period.

If the eye meets the criteria for additional treatment being "apparently futile", the treating ophthalmologist may elect to discontinue further treatment at this visit. However, the treating ophthalmologist is not obligated to discontinue treatment at this visit and may perform an additional treatment (either laser photocoagulation or intravitreal triamcinolone injection, according to the randomization assigned treatment) if desired.

Example of "Apparently Futile" at 20 Months After Study Enrollment

An eye improved in visual acuity from 55 letters (approximately 20/80) to 70 letters (approximately 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 70 letters (approximately 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 70 letters (approximately 20/40) and the smallest OCT thickness measured was 290 (less than 50 microns reduction from 300 microns measured at 12 months). 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 or more months 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 with BRVO and without a dense macular hemorrhage who have received laser photocoagulation.

4.8.4 Alternate Treatment for the Study Eye

Although it is preferable that study eyes assigned to standard care (i.e., laser photocoagulation for BRVO eyes without a dense macular hemorrhage or observation for CRVO eyes or observation for BRVO eyes with a dense macular hemorrhage) not be treated with intravitreal triamcinolone acetonide and for study eyes assigned to intravitreal triamcinolone acetonide not be treated with laser photocoagulation, it is recognized that there may be situations where the investigator strongly believes that the alternate treatment should be provided.

An eye may be treated with the alternate 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 a standard care group may receive (but is not required to receive) intravitreal triamcinolone (4 mg dose, study formulation) and BRVO eyes without a dense macular hemorrhage assigned to intravitreal triamcinolone injection may receive (but are not required to receive) laser photocoagulation. When the above criteria are met, the investigator should only provide the alternate treatment if the investigator strongly believes that the alternate treatment is in the patient's best interest.

4.8.5 Other Treatments

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

4.9 Diagnosis and Treatment of Adverse Events

4.9.1 Endophthalmitis Treatment

The decision to treat a patient for an endophthalmitis or a suspected endophthalmitis will be guided by the clinical judgment of the investigator. The treatment method (pars plana vitrectomy vs. vitreous tap) and choice of antimicrobial agents is also at the discretion of the investigator and should follow current standard practice patterns. The decision to use intravitreal steroids (e.g. dexamethasone) for the treatment of endophthalmitis is also at the discretion of the investigator.

4.9.2 Treatment of Elevated Intraocular Pressure (IOP)

It is expected that some patients will have an IOP rise that may require treatment to lower the IOP.

Treatment of elevated IOP will be instituted whenever the IOP is greater than or equal to 30 mm Hg. The treatment to prescribe will be at investigator discretion and may include referral to another ophthalmologist. If the IOP is between 22 and 30 mm Hg, then the IOP should be measured again within one month and treated if greater than or equal to 30 mm Hg. IOP greater than 25 mm Hg at consecutive 4-month visits should be treated. If IOP is greater than 25 mm Hg for 4 months, then a visual field should be performed to evaluate for glaucomatous damage.

The treatment to prescribe is at the discretion of the investigator and may include referral to another ophthalmologist. One treatment regimen that can be followed was used in the Collaborative Initial Glaucoma Treatment Study[53] and is listed below:

Participants may receive a sequence of medications, which may begin with a topical beta-blocker, followed by an alternate single topical therapeutic agent, dual topical therapy, triple topical therapy, an alternate combination of triple topical therapy, and an optional additional topical and/or oral medication or medications. If further treatment is required, the next treatment step may be argon laser trabeculoplasty, followed by trabeculectomy, medication, trabeculectomy with an antifibrotic agent, and medication.

4.9.3 Cataract Surgery

It is expected that some study participants in both the intravitreal steroid arms and the standard care arms will develop cataract within the study period. The decision to perform cataract surgery is at 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):

Indications for Cataract Surgery:

1. Visual function that no longer meets the participant's needs and for which cataract surgery provides a reasonable likelihood of improvement.
2. Lens opacity that inhibits optimal management of posterior segment disease.
3. The lens causes inflammation (phakolysis, phakoanaphylaxis), angle closure, or medically unmanageable open-angle glaucoma.

*Participants in **both** the intravitreal steroid groups and the standard care groups should be assessed for the development of cataract in a similar fashion. Cataract surgery may be performed at any time that this is indicated clinically.*

4.9.4 Surgery for Proliferative Retinopathy and Other Complications Due to Retinal Vein Occlusion

It is expected that some study participants will develop vitreous hemorrhage and/or other complications of retinal vein occlusion that may cause visual impairment. Vitrectomy for the complications of proliferative 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 steroids such that participants assigned to the steroid treatment arms may experience reduced benefit from intravitreal steroid injections following vitrectomy.

A suggested treatment plan that may be followed for eyes with vitreous hemorrhage and/or other complications of retinal vein occlusion 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.
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 vitreomacular traction or an epiretinal membrane can, at the discretion of the investigator, 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.

4.10 Miscellaneous Treatments During Follow-up

4.10.1 Treatment of Macular Edema in Non-study Eye

If a non-study eye that was not eligible for enrollment develops macular edema associated with retinal vein occlusion requiring treatment, the treatment will depend on the randomization group of the study eye. The following also applies to the non-study eye of a patient who presents with both eyes eligible for the SCORE study at screening and when both eyes have the same disease (CRVO or BRVO) or if each eye has a different disease (i.e. one eye has a CRVO and the other eye has a BRVO).

- If the study eye was assigned to an intravitreal corticosteroid group, then the non-study eye will receive standard care to avoid treating both eyes with intravitreal corticosteroids.
- If the study eye was assigned to standard care, then the non-study eye may be treated with either intravitreal corticosteroids *(study preparation, 4 mg dose only)* or standard care at investigator/patient discretion. A non-study eye treated with the study steroid preparation will undergo the same follow-up schedule, retreatment regimen and adverse event monitoring as study eyes in the SCORE Study.

4.10.2 Panretinal Photocoagulation (PRP) Treatment:

PRP or sector PRP can be given if it is indicated in the judgment of the investigator and following guidelines established by the CVOS and BVOS. Recall that participants are not eligible for the SCORE Study if, at the time of randomization, it

is expected that they will need PRP within 4 months. The following guidelines should be followed:

Burn Characteristics

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
Wavelength	Green to yellow *(red can be used if vitreous hemorrhage is present precluding use of green or yellow)*

5. Data Monitoring and Adverse Event Reporting

5.1 Data Safety Monitoring Committee

The SCORE Data and Safety Monitoring Committee (DSMC) is responsible for reviewing the study design and, as appropriate, recommending design changes to the SCORE Executive Committee and the NEI. The DSMC also may recommend to the NEI to suspend enrollment if adverse events predominate. In addition, the DSMC assesses study data, particularly for adverse and/or beneficial effects of treatment. The DSMC is expected to meet at least every six months and will review all accumulating study data including adverse events. The SCORE Data Coordinating Center (DCC) will report to the DSMC expeditiously, on a case-by-case basis, specific adverse events described in the DSMC Standard Operating Procedure document. In addition, the DSMC will review early safety data on patients from the SCORE Study and from the Diabetic Retinopathy Clinical Research Network (DRCR.net) study on intravitreal triamcinolone and diabetic macular edema. Both studies are served by the same DSMC and both studies will use the same drug

formulation. The SCORE Study will not proceed if there are any serious concerns identified with the formulation or the injection procedure. The monitoring plan that the DSMC will follow is:

- An initial report will include the day 4 follow-up data from the first 5 patients (combined in the DRCRnet and SCORE studies) who receive an intravitreal triamcinolone injection. No additional patients will receive an intravitreal injection until these data have been obtained and it is clear that there are no immediate safety concerns.
- A second report will be compiled after 5 patients have completed the 4-week post injection exam. It will include the 4-day data on a second group of 5 patients. Note: no more than 10 patients will receive intravitreal injections until the first 5 patients have completed at least 4 weeks of follow up. Thereafter, assuming that there have not been any unexpected consequences of the injections, enrollment will be opened to all sites.
- A third report will be compiled after 10 patients who receive an intravitreal triamcinolone injection have completed the 4-week post injection exam.

Thereafter, assuming that there have been no safety concerns, the data will be reviewed on a monthly basis by the DSMC until the committee is comfortable with reviewing the data on a less frequent schedule.

5.2 Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

Each clinical site is responsible for reporting all adverse events, including toxicities, that occur to SCORE participants enrolled at their site, regardless of relatedness to study therapy or procedure. Reporting of all adverse event data is expected upon recognition.

Serious adverse events (SAEs), as defined in Section 5.3.1.2 **must** be reported to the SCORE DCC within 24 hours of recognition. Study investigators must report serious adverse events to their local ethics review committee (or IRB) promptly in accordance with local regulations or policies in addition to the SCORE DCC. The SCORE DCC may request additional information regarding adverse events from investigators following their initial review.

5.3 Procedures for Reporting Adverse Events

Clinical sites are required to report all adverse events via the SCORE electronic data capture system (AdvantageEDC^{SM}). Each site will receive training on reporting requirements. Electronic forms that are designed to collect adverse event data will be available for input at any time, including between scheduled visits.

When a reported adverse event is determined to be serious, unexpected, and to have a reasonable possibility to be related to the test product or procedure, or otherwise reportable to regulatory agencies or drug manufacturers, the SCORE DCC will prepare an initial report as described below. Cumulative reports of other adverse events not considered serious will also be prepared by the SCORE DCC and reviewed by the Medical Monitor on at least a monthly basis, and by the DSMC on a routine basis at least semi-annually.

5.3.1 Routine SCORE DCC Review

The SCORE DCC Medical Monitor will be provided relevant material in order to assess whether there are safety concerns that may require expedited reporting to the FDA, DSMC, local ethics committee (or IRB), study investigators, the pharmaceutical manufacturer, or the study sponsor (National Eye Institute). A report of new adverse events will be reviewed each weekday by the SCORE DCC. Other data are reviewed weekly by the SCORE DCC.

5.3.1.1 Definition of Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

- Unexpected Adverse Drug Reaction – An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert / summary of product characteristics for an approved product.).

Throughout the study, all adverse events must be recorded in the AdvantageEDC, regardless of the severity or relationship to study medication or procedure. If an adverse event is caused by a combination of treatment and disease, the adverse event should be graded as it is observed. Early in the development of a therapy, when little is known about the therapy's safety profile, it is especially important to maintain a high level of suspicion and report adverse events that may be treatment-related adverse events. This reporting may facilitate identification of idiosyncratic or low frequency treatment-related adverse events.

5.3.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any adverse event occurring at any dose that results in any of the following outcomes:

a. Death;
b. Life-threatening adverse event*;
c. In-patient hospitalization or prolongation of existing hospitalization;
d. Persistent or significant disability / incapacity;
e. Congenital anomaly / birth defect.

** Including any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).*

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when,

based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.3.1.3 Expected and Unexpected Adverse Event

All adverse events, be they routine or serious, will be classified as either expected or unexpected. Any adverse therapeutic experience that is associated with the study therapy or procedure and is listed as such in an investigational plan, investigational brochure, protocol or informed consent is an expected event. In contrast, any adverse therapeutic experience, the specificity or severity of which is **not** consistent with the investigational plan, investigator brochure, protocol, or informed consent for the therapy is an unexpected event.

5.3.2 Adverse Event Severity Grading

Severity grades are assigned by the study site to indicate the severity of all adverse experiences. The SCORE Study has adapted usage of The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) for application in adverse event reporting. A copy of the CTCAE system can be found on the SCORE website: (http://www.emmes.com/).

The CTCAE provides a term and a grade that closely describes the adverse event. The CTCAE grade for each adverse event should be associated with a severity category: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-threatening) and Grade 5 (Death). If the adverse event is not included in the CTCAE, the following general definitions should be used in determining severity:

Grade 1 Mild Transient or mild discomforts (<48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (nonprescription or single-use prescription therapy may be employed to relieve symptoms, e.g.,

		aspirin for simple headache, acetaminophen for post-surgical pain). Mild adverse effects are an expected consequence of the SCORE protocol used here, and standard supportive therapies (per institutional guidelines) are permitted.
Grade 2	**Moderate**	Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
Grade 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required, hospitalization or hospice care probable.
Grade 5	**Death**	Death.

5.3.3 Relation to Therapy

The *physician* acting as the Principal Investigator at each study site or his/her *physician designee* should make the determination of therapy-relatedness of an adverse experience. A therapy-related determination must be made for every adverse event, regardless of severity or event type (routine AE or SAE). A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the study drug.

5.3.4 Adverse Event Reporting Requirements and Procedures for Clinical Sites to the SCORE Coordinating Center

All adverse events, deaths, infections, and hospitalizations, regardless of severity, expectedness, or potential association with the investigational drug, will be entered on the appropriate form in the AdvantageEDC.

5.3.4.1 Requirements

Clinical sites are required to enter all known adverse event data from all events into the electronic adverse event form in the AdvantageEDC.

Serious adverse events are required to be entered into the AdvantageEDC within 24 hours of recognition. If all information required on the event form has not been obtained, the site should submit what is available. Additional information, as it becomes available, can be submitted at a later date.

5.3.5 Reporting Procedures

For reporting of AEs and SAEs, the Site Coordinator will:

1. Complete an Adverse Event form (page 1) in the SCORE data entry system.
2. If the site determines that the event is **serious**, the site will complete, in detail, the Adverse Event Summary (page 2 of the Adverse Event Form).
3. The SCORE Medical Monitor will review the Adverse Event Summary and complete an Adverse Event Review form (page 3 of the Adverse Event form).
4. If follow-up information is required, the SCORE DCC will contact the site.
5. If rapid reporting is required, the SCORE DCC will prepare a MedWatch and forward copies of the completed MedWatch to the SCORE Study Chair and Co-Chair, DSMC Chair, and IND sponsor who will send the MedWatch to the FDA.

5.3.6 SCORE Adverse Event Reporting Contact

The SCORE Project Director (listed in the Data Management Handbook as well as the current MOPP) may be contacted at the SCORE DCC, The EMMES Corporation, located in Rockville, Maryland. Be sure to clearly indicate the protocol number and the location of your site when contacting the SCORE DCC. Back-up personnel and procedures are in place to assure that if the Project Director is not available, other

personnel at the SCORE DCC can adequately handle requests or adverse event reporting requirements. For urgent AE requests that occur after business hours (8:30 – 5:00 Eastern Time), contact:

Maria Figueroa, MBA, CCRP
SCORE Project Director
The EMMES Corporation
Tel. (240) 344-1935

5.4 Procedure for Reporting of Pregnancy

At the time a site Principal Investigator or Study Coordinator becomes aware that a study participant has become pregnant during the study, the Principal Investigator or Study Coordinator will prepare a report on the pregnancy to be sent to the SCORE DCC that includes the following elements:

- Participant (mother's) coded study identifier(s);
- Date of last menstrual period;
- Date of enrollment;
- Date(s) of fluorescein angiogram(s); and
- Date of last intravitreal injection or laser treatment, if any.

Any pregnancy that occurs during the study should be followed until the time of delivery, miscarriage or abortion. A report with any relevant information on the condition of the fetus or infant at birth should be forwarded to the SCORE DCC, including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage, or abortion;
- Birth weight, gender, length, and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities. Report all abnormalities as a serious adverse event.

6. Statistical Considerations

6.1 Scientific and Regulatory Objectives

The SCORE Study's scientific and regulatory objectives are to compare the efficacy and safety of standard care with intravitreal injection(s) of triamcinolone acetonide (4 mg or 1

mg) to treat macular edema associated with CRVO and BRVO. Although scientific goals parallel regulatory goals, regulatory requirements demand some divergence of scientific statistical methods from regulatory statistical methods for testing the null hypothesis of no treatment effect of triamcinolone acetonide. Section 6.2 describes the formal test to be performed for drug registration, while the remaining sections describe the scientific statistical approach. The DSMC will be responsible for monitoring the SCORE Study following the scientific plan only.

6.2 Formal Regulatory Statistical Test of Efficacy

For regulatory purposes, the SCORE Study will be configured as two separate and independent clinical trials "A" and "B", each trial to serve as confirmatory of the other. To accomplish this, clinical sites will be allocated before recruitment commences to either trial "A" or trial "B", using a method that strives for comparable geographic patterns and distributions of enrollees per center. Within each trial, CRVO and BRVO disease areas will be pooled for analysis and three primary efficacy analyses performed after no more than one year of follow-up. A detailed description of the method of assigning sites to Trial "A" and Trial "B" is provided in the SCORE Study Manual of Procedures and Policies (MOPP). The assignment of sites to Trial "A" and Trial "B" will be made prior to recruitment of subjects. One analysis will compare 1 mg steroid versus standard care, one will compare 4 mg steroid versus standard care, and one will compare 1 mg versus 4 mg steroid. The comparison will be with respect to the primary outcome measure. The primary outcome measure indicates whether or not a study eye of a participant experiences an improvement of 15 or more letters from baseline in best-corrected ETDRS visual acuity score. The significance of the three comparisons will be obtained by Hochberg's sequentially rejective procedure, as described in detail in the MOPP, section 6.2. The overall alpha for the A trial will be no more than 0.05, and similarly for the independent B trial (more specifically, the alpha for each of the "A" and "B" trials will be diminished from 0.05 by the amount of alpha previously spent on interim scientific efficacy assessments). Within trial "A" and within trial "B", an initial analysis of treatment effect will be carried out by logistic regression to determine whether a statistical interaction exists between disease group (BRVO and CRVO) and treatment group (standard care, 4 mg steroid, and 1

mg steroid). A finding of no interaction effect will provide justification for pooling the CRVO and BRVO participants within trial "A" and trial "B" and the primary efficacy analyses for regulatory purposes, as described above, will be carried out by means of logistic regression adjusting for disease area, baseline visual acuity, and center. A statistically significant interaction effect will require separate primary efficacy analyses for CRVO and for BRVO within trial "A" and with trial "B".

6.3 Scientific Statistical Approach

6.3.1 Two Independent Clinical Trials

The SCORE Study consists of two separate independent clinical trials - one for CRVO and one for BRVO. Each of these clinical trials has its own overall Type I error (alpha) = .05.

6.3.2 Three Primary Questions in Each Clinical Trial

Each of these clinical trials asks three questions. One question is the comparison of standard care to 4 mg intravitreal injection(s) of triamcinolone acetonide. A second question is the comparison of standard care to 1 mg intravitreal injection(s) of triamcinolone acetonide. The third question compares 1 mg to 4 mg intravitreal injections. Within each clinical trial, the significance of the comparisons will be obtained by Hochberg's sequentially rejective procedure using an alpha level of 0.05 (see the MOPP, section 6.4).

6.3.3 Primary Efficacy Outcome Measure and Time Point

Improvement by 15 or more letters from the randomization visit visual acuity to the 12-month follow-up visual acuity is the primary efficacy outcome measure. Visual acuity is to be measured using E-ETDRS visual acuity testing.

6.3.3.1 Primary Efficacy Analysis Method

The three treatment comparisons (1 mg versus standard care, 4 mg versus standard care, and 1 mg versus 4 mg) will be made by means of logistic regression adjusting for baseline visual acuity, clinical site, and presence of baseline macular hemorrhage in participants with BRVO. The test statistic

will be compared to the critical value of the efficacy monitoring guideline (section 6.7.2). Family-wise error will be controlled at no more than 0.05 by Hochberg's sequentially rejective method, modified for interim monitoring as specified in the MOPP.

The analysis will be on the basis of intent to treat (ITT), treating missing observations as missing completely at random [i.e., missing data from study participants will be dropped from the analysis and noncompliance (or treatment crossover) ignored].

6.3.3.2 Additional Analysis Methods for Consistency of Primary Efficacy Result

We will investigate two other ITT variants: (1) last-observation-carried-forward (LOCF) and (2) performing a sensitivity analysis in which outcomes will be assigned to missing eyes so as to explore both the minimum and maximum possible estimates of treatment effects. A per-protocol analysis, excluded from which will be those study participants who drop out, cross over to another treatment group, or violate the protocol, also will be conducted including only study eyes that have completed 12-month visual acuity data. Logistic regression analysis will be performed to adjust for any potential imbalances in baseline characteristics observed between treatment groups, with the odds ratio used as a measure of increased or decreased risk. Important baseline differences, not necessarily based on tests of statistical significance, will be investigated as to their ability to confound the association between the treatment groups and the primary outcome. Although the intent-to-treat analysis described in section 6.3.3.1 is considered to be the definitive analysis, these additional analyses (e.g. other ITT variants, per-protocol) will be used to explore the consistency of the result and provide more information as to the benefit or lack of benefit of the treatment.

6.4 Assumptions for and Result of Sample Size Estimation

6.4.1 Study Power

The study power is set for each trial at 80%.

6.4.2 Estimate of CRVO Primary Efficacy Outcome in the Standard Care Group

The Central Vein Occlusion Study (CVOS) demonstrated that in participants with macular edema for more than 3 months secondary to a CRVO, macular grid laser photocoagulation, as compared to no treatment, did not improve visual acuity.[4] There were no significant differences between treated and untreated participants in either level of visual acuity or change in visual acuity across all follow-up visits. The data from the CVOS demonstrate that at 2 years from baseline 18% of treated eyes (10 of 57 eyes) and 11% of untreated eyes (6 of 53 eyes) experienced a gain of three or more lines of visual acuity. At 1 year, approximately 6% in both the treated and untreated eyes showed a gain of three or more lines of visual acuity. From these data, it is conservatively estimated that approximately 15% of untreated eyes with CRVO will experience a gain of three or more lines of visual acuity at 1 year.

6.4.3 Estimate of BRVO Primary Efficacy Outcome in the Standard Care Group

In the Branch Vein Occlusion Study (BVOS), macular grid laser photocoagulation was demonstrated to be effective in improving visual acuity in some eyes with BRVO complicated by macular edema.[1] Treatment resulted in a two or more line improvement in visual acuity for two or more consecutive visits in approximately 45% of eyes at the 2-year follow-up. At one year, approximately 20% of treated eyes gained two or more lines of visual acuity at two or more consecutive visits. Patients in the BVOS all had absence of dense macular hemorrhage before enrollment. In the SCORE Study, we anticipate as many as 50% of participants may have a dense macular hemorrhage at enrollment and therefore will have grid laser treatment postponed until the hemorrhage clears to permit treatment. It is uncertain how the inclusion of these eyes will affect efficacy in the standard care arm of the SCORE study. From these data, it is conservatively estimated that approximately 35% of

standard care eyes will experience a gain of three or more lines of visual acuity at 1 year.

6.4.4 Background Information on Efficacy of Intravitreal Injection(s) of Triamcinolone Acetonide

In Table 4, we provide outcomes of treatment with intravitreal steroid injections based on six published reports of case series. Data concerning diabetic macular edema (DME) are included because of the similarity (VEGF related vascular permeability) between DME and macular edema due to retinal vein occlusion.

Table 4

	# of eyes treated	Disease	Dose (mg)	Anatomical improvement	Mean baseline visual acuity	Mean visual acuity at endpoint	Follow-up (mos)
Martidis[33]	16	DME	4	11/16 (69%)	20/200	20/80	3
Jonas[41]	26	DME	25	21/21 (FA)	20/160	20/100	6.6
Jonas[37]	2	CRVO	25	2/2 (100%)	20/160	20/125	3
Greenberg[35]	2	CRVO	4	2/2 (100%)	20/400	20/160	4.5
Ip[36]	2	CRVO	4	1/2 (50%)	20/200	20/100	6
Park[38]	10	CRVO	4	10/10 (100%)	20/80	20/32	4.8

Except for Park et al,[38] the six case series above did not use standardized methods to measure visual acuity. However, all six studies indicate a high likelihood of significant visual acuity improvement for treatment of macular edema with intravitreal triamcinolone acetonide. The report by Martidis[33] showed 11 of 16 DME eyes (69%) having a 3-line improvement in visual acuity at the last follow-up visit for each eye, which was either 3 or 6 months after the intravitreal injection. Park et al[38] showed that 7/10 (70%) had a 3 or more line improvement after a mean of 4.8 months follow up. Further, unpublished data (Martidis et al and Ip et al), some of which were presented at the 2002 Retina Congress (San Francisco, CA),

provide additional evidence of the efficacy of this treatment for macular edema secondary to retinal vein occlusion and diabetic macular edema. Martidis et al, at the 2002 Retina Congress, reported additional information on efficacy for DME: 73/125 (58%) had a two or more Snellen line improvement at an average follow-up of 6.7-months. For BRVO with prior laser treatment, 6/13 (46%) had a three or more Snellen line improvement at 6 months. Ip et al, at the 2002 Retina Congress, reported additional information on efficacy for CRVO (three Snellen line improvement): 3/8 (38%) had a three or more Snellen line improvement at 6 months.

6.4.4.1 Estimate for CRVO Primary Efficacy Outcome in the Intravitreal Injection(s) Groups

For CRVO eyes, our projected rate of improvement of 15 or more letters at one year is 30% in the 1 mg and in the 4 mg injection group.

6.4.4.2 Estimate for BRVO Primary Efficacy Outcome in the Intravitreal Injection(s) Groups

For BRVO eyes in the SCORE Study, in which all eyes will not have had prior laser treatment, we expect efficacy for eyes receiving intravitreal injection(s) of triamcinolone to be higher, and project 53% will have an improvement of 15 or more letters at 1 year in the 1 mg and in the 4 mg group.

6.4.5 Sample Size Estimate

The sample size estimate (number per group) was computed assuming the efficacy in the two steroid doses are the same. If the efficacy in the 4 mg group is higher than the 1 mg group, and given the other preceding assumptions, the study power will be higher for the standard care versus 4 mg comparison. This was considered important because the 4 mg dose is the basis for all available information.

Sample Size Estimate

Type I error (alpha) = .025, study power = 80%

	CRVO	BRVO
Standard care	15%	35%
1 mg or 4 mg	30%	53%
N per group	147	147

The allocation ratio will be 1:1:1 for standard care: 1 mg: 4 mg. The number per group has been increased by 10% to allow for some missing data at 12 months (number per group=162). Thus, the total sample estimate for the CRVO trial is 486 (3 times 162) and for the BRVO trial the total sample estimate is 486 (3 times 162).

6.5 Safety Outcomes

Safety outcomes that will be assessed include serious adverse events and specific ocular events requested by the Data and Safety Monitoring Committee. The SCORE Study DCC and DSMC will continuously monitor the following safety indicator variables:

- Cataract
- IOP exceeding 35 while on maximal medical therapy
- Filtration surgery to lower IOP
- Non-infectious endophthalmitis
- Any of: infectious endophthalmitis, retinal detachment, vitreous hemorrhage, loss of 20 ETDRS letters at 4 days or 4 week post injection, a new-onset retinal arterial occlusion, a transition from a branch to a central retinal vein occlusion, a new, clearly independent branch retinal vein occlusion, or anterior ischemic optic neuropathy.

Table 5 indicates the precision with which the SCORE Study will be able to estimate rates of safety events at the end of the trial. Three sample sizes are provided in Table 5:

- N=162: within each study arm.
- N=324: pooling the 1 mg and 4 mg intravitreal injection arms <u>within</u> CRVO or BRVO disease area OR pooling the 1 mg or 4 mg intravitreal injection arm <u>across</u> each disease area.

- N=648: pooling the 1 mg and 4 mg intravitreal injection arms across each disease area.

For example, if the true rate is 0.25 and the sample size is 162, the 10% quantile for the lower 95% confidence limits is 0.15, and the 90% quantile for the upper 95% confidence limit and half-width are 0.36 and 0.07, respectively.

Table 5: 90% limits for 95% confidence intervals of rates of safety events, as a function of the true rate *p* and the sample size *N*

	N=162			*N*=324			*N*=648		
P	**Lower CL**	**Upper CL**	**Half width**	**Lower CL**	**Upper CL**	**Half-width**	**Lower CL**	**Upper CL**	**Half-width**
0.01	0.00	0.05	0.02	0.00	0.04	0.02	0.00	0.03	0.01
0.03	0.00	0.09	0.04	0.01	0.07	0.02	0.01	0.06	0.02
0.05	0.01	0.13	0.04	0.02	0.10	0.03	0.03	0.08	0.02
0.1	0.03	0.19	0.05	0.05	0.16	0.04	0.06	0.14	0.03
0.15	0.07	0.25	0.06	0.09	0.22	0.04	0.11	0.20	0.03
0.25	0.15	0.37	0.07	0.18	0.33	0.05	0.20	0.31	0.03
0.5	0.37	0.63	0.08	0.41	0.59	0.06	0.44	0.57	0.04

6.6 Secondary Efficacy Outcomes

Secondary efficacy outcomes will be analyzed by comparing each triamcinolone group (4 mg or 1 mg) to standard care as well as by comparing 4 mg vs 1 mg intravitreal triamcinolone for the secondary efficacy outcome variables listed below. The secondary efficacy outcomes include the following:

- Change between baseline and each efficacy outcome assessment visit in best-corrected ETDRS visual acuity score (e.g., mean change from baseline in visual acuity, distribution of change from baseline in visual acuity based on clinically meaningful cut points of improvement or worsening of visual acuity).
- Change in calculated retinal thickening as assessed by optical coherence tomography.
- Change in retinal thickness at the center of the macula as assessed by stereoscopic color fundus photography.
- Change in area of retinal thickening as assessed by stereoscopic color fundus photography.

6.7 Statistical Guidelines for Interim Monitoring by the DSMC

6.7.1 Interim Monitoring for Safety

The SCORE Study will use repeated confidence intervals to continuously monitor the safety indicator variables mentioned in section 6.5. Safety rates will be reported separately in the two disease areas, but injection arms will be pooled to increase accuracy of the estimates.

6.7.2 Interim Monitoring for Efficacy

The primary efficacy outcome occurs at 12 months from the randomization visit. The recruitment pattern is unpredictable. Information concerning the primary outcome will accrue as participants complete their 12-month visit and thus "information time" is the percent of the 486 patients in each trial expected to have completed this visit.

Of the Type I error (alpha) = .05 for each trial, alpha = 0.005 will be allocated for interim monitoring and the remaining alpha = 0.045 will be reserved for the final analysis. With alpha =0.045 for the final analysis, the estimate of the sample size does not need to be increased for interim monitoring. Interim testing will be carried out using the Lan-DeMets interim monitoring boundary with an O'Brien-Fleming-type spending function where at most 0.005 cumulative alpha can be spent prior to the final analysis. The "height of the hurdle" is highest when the information fraction is smallest and decreases as additional patients complete 12 months. The "height of the hurdle" can be calculated for each DSMC meeting based on the number of patients expected to have completed the 12-month visit and the alpha spent by previous "looks" by the DSMC. With the specification that the total alpha for interim monitoring is 0.005, the maximum amount the DSMC can "spend" is 0.005. If the DSMC looks more often, it will "spend" less per look.

Formally, if *t* is the information fraction, *B(t)* is the 2-sided cumulative O'Brien-Fleming-type spending function of Lan & DeMets with final value *B(1)* = 0.005, and *S(t)* is the two-sided cumulative spending function used by SCORE, then

$$S(t) = \begin{cases} B(t) \text{ for } 0 \le t < 1 \\ 0.05 \text{ for } t = 1 \end{cases}$$

At each interim inspection, the three comparisons will be made using the Lan-DeMets methodology, and the results combined using Hochberg's sequentially rejective procedure as described in the MOPP, section 6.4.

6.7.3 Interim Monitoring for Futility

The DSMC will consider futility as well as safety and efficacy. One method of statistically assessing futility is to use conditional power to estimate the likelihood of statistical significance given the observed efficacy results and various possible choices for the remaining results.

6.7.4 Analyses and Results Requested to be Considered Prior to Recommending Early Termination

Before recommending early termination, the DSMC will consider:

- internal consistency of primary and secondary results
- internal consistency of primary and secondary results by subgroups defined by baseline characteristics (e.g. visual acuity categories, categories based on length of history of CRVO or BRVO, and time period of enrollment)
- distribution of baseline prognostic factors among the three groups (standard care, 4 mg, 1 mg)
- consistency of primary and secondary results across clinical centers and among centers enrolling larger numbers of patients

- possible bias in assessment of primary and secondary response variables, particularly visual acuity, given the unmasked implementation of standard care versus intravitreal triamcinolone
- possible impact of missing data from missed patient visits for assessment of the primary and secondary response variables
- possible differences in concomitant interventions or medications.

6.7.5 Study Timeline and DSMC Data Reviews

The DSMC will meet to review study data starting in November 2004, and every 6 months until 3-year follow-up is concluded on all study participants. Table 6 depicts the fractions of the population enrolled, with 1 year follow-up, and with 3 year follow-up, assuming that enrollment is constant, starts in August 2004, and takes 18 months. Under this assumption, there will be 10 DSMC meetings. Formal interim inspection for 1-year efficacy will take place only during the four meetings when the information fraction is nonzero, that is, in November and May of 2005 and 2006.

Table 6: Study Timeline for DSMC Data Reviews

Date of DSMC Meeting	Fraction		
	Enrolled	With 1-year follow-up	With 3-year follow-up
November 2004	2/9		
May 2005	5/9		
November 2005	8/9	2/9	
May 2006	1	5/9	
November 2006		8/9	
May 2007		1	
November 2007			2/9
May 2008			5/9
November 2008			8/9
May 2009			1

7. Confidentiality and Access to Source Data / Documents

The investigators will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants in this clinical study. Medical and research records should be maintained in the strictest confidence. However, as part of the quality assurance and legal responsibilities of an investigator, the site must permit authorized representatives of the sponsor(s), the SCORE Coordinating Center, and regulatory agencies to examine (and when permitted or required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the law, no copying of records with personally identifying information will be permitted. Only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information) or transmitted to the SCORE Coordinating Center. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. The site will normally be notified in advance of monitoring and auditing visits.

8. Summary of Good Clinical Practice Compliance

This trial will be conducted in accordance with Good Clinical Practice (GCP) using the guidance documents and practices offered by ICH and FDA, and in accordance with the Declarations of Helsinki and the policies and procedures for the SCORE Coordinating Center at The EMMES Corporation. This study will also comply with the regulations under 21 CFR Parts 50, 54, 56, and 312 under an IND application authorized by FDA.

8.1 Investigator Responsibilities (Form FDA-1572)

A Statement of Investigator (Form FDA-1572) including the names of all of the sub-investigators and selected key study personnel (e.g., pharmacist, study nurse and/or study Coordinator, ophthalmic technician or optometric staff may be listed if desired) directly involved in the study will be completed and signed by the Principal Investigator at each site. The general responsibilities of the Investigator as acknowledged on the Form FDA-1572 are governed under the regulations in 21 CFR Parts 50, 54, 56, 312, and HIPAA. The study drug or test article may be administered only in accordance with the approved protocol and under the supervision of the Investigator or a sub-investigator listed on this

form. The Investigator must maintain accurate and complete study records, including records for disposition of the test article, and an accurate and complete record of all submissions made to and received from the local Institutional Review Board (IRB) or Independent Ethics Committee (IEC), including a copy of all reports and documents submitted. Adverse experiences that are reported to the FDA as IND Safety Reports must be submitted promptly to the local IRB/IEC and the SCORE Coordinating Center.

Progress reports must be submitted by the Investigator to the IRB/IEC at least once per year. The IRB/IEC must be promptly notified of completion or termination of the study. Within three months of study completion or termination, a final report from the Investigator must be provided to the IRB/IEC.

The curriculum vitæ (CV) or a résumé for each investigator, sub-investigator, and key study personnel must also be supplied if named on the Form FDA-1572. This form and related CVs must be supplied to the SCORE Coordinating Center prior to initiating the trial at each site. When necessary due to personnel changes, updated versions of the Form FDA-1572 must be forwarded to the SCORE Coordinating Center and copies of all versions must be maintained in study records at each site. Any CV or résumé collected at the beginning of a study should be current, and would need to be updated during the study only if substantial changes or additions are warranted (e.g., change of position or affiliation, certifications or licensure, or significant new publications relevant to the study protocol).

8.2 Human Subjects Protection

8.2.1 Institutional Review Board or Independent Ethics Committee

Each participating institution must have an IRB or IEC constituted and operating in accordance with the regulations under 21 CFR Part 56 and authorized by the institution to review and approved materials for this trial. Because of the use of US Federal funds in this trial, all participating institutions must have a current Assurance of Compliance (either FWA or MPA) regarding their IRB/IEC on file with the DHHS Office of Human Research Protections (OHRP) before any award can be made to that

institution and before participants may be enrolled in the trial. In addition, each reviewing IRB or IEC must be registered with OHRP. A list of IRB/IEC voting members, their titles or occupations, and their institutional affiliations, as well as a copy of the Assurance of Compliance, must be kept available by the institution for inspection and copying by authorized study monitors, auditors, and regulatory officials.

8.3 Data Handling and Recordkeeping

The Principal Investigator at the Participating Clinical Center is responsible for maintaining adherence to study procedures within the clinic. He or she must spend adequate time at the clinic observing study procedures and must hold regular discussions with staff, either one-to-one or in-group meetings, to review various aspects of the study and to solve problems that may arise. Other clinic staff members have a responsibility to report to the PI problems that could affect the quality of the data. The PI will designate one staff member to be the Clinic Coordinator for the clinic, with specific responsibility for reporting problems that have affected or can potentially affect the quality of data collected.

The Clinic Coordinator should be thoroughly familiar with clinic activities and equipment and the MOPP. The Clinic Coordinator should maintain an up-to-date copy of the MOPP close at hand and encourage all clinic personnel to consult it frequently. During Full Group Meetings the Clinic Coordinators will have the opportunity to meet with the Protocol Monitor to discuss mutual problems.

8.3.1 Case Report Forms

Clinical data will be entered on electronic Case Report Forms (CRFs) in accordance with the procedures specified in the current MOPP and Data Management Handbook (DMH) for this trial.

8.3.2 Data Transmittal

The primary method of data transmittal to the SCORE Coordinating Center will be via the secure AdvantageEDC maintained by The EMMES Corporation. The current

MOPP, DMH and access to the AdvantageEDC are available to authorized users via the SCORE DCC Internet web site, located at http://www.emmes.com/ where an assigned username and password are required for access. All data transfers between the investigational site and SCORE DCC via the AdvantageEDC are encrypted using SSL technologies to assure confidential data transfer.

8.4 Professional Licensure

Physicians must provide evidence of current medical licensure applicable to the study location(s) if they are practicing medicine and undertake to diagnose and/or treat participants (including administration of the test article) in this study. A physician who is a site Principal Investigator must also provide evidence of ophthalmology training before study initiation.

8.5 Human Subjects Protection Training

Documented training is required for each of the key personnel in the ethical conduct of clinical studies and in the protection of human subjects.

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10. Appendix I

Appendix 1: Scheduled Study Evaluations

	Baseline	4-month interval follow-up visits									Safety[2]	
		M4	M8	M12	M16	M20	M24	M28	M32	M36	D4	M1
Informed consent	X											
Urine pregnancy test	X[3]											
Medical/ocular history	X[3]											
Blood pressure	X[3]			X			X			X		
Visual acuity	X[4,5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[7]	X[7]
Manifest refraction	X[5]	X[5]		X[5]			X[5]			X[5]		
IOP	X[3,5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[7]	X[7]
Ophthalmic examination[8]	X[3,5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[7]	X[7]
Lens assessment[9]	X[3,5]	X[5]		X[5]			X[5]			X[5]		
Fundus photos												
Study Eye	M7F[3]	M3F	M3F	M7F	M3F	M3F	M7F	M3F	M3F	M7F		
Non-study Eye	M3F[3]			M3F			M3F			M3F		
FA	X[3]	X		X			X					
OCT	X[5,10]	X[5]	X[6]	X[5]	X[6]	X[6]	X[5]	X[6]	X[6]	X[5]		
Steroid injection /Laser[1]	X	X	X	X	X	X	X	X	X			

M= month
Q= every
D= day

M7F= Modified 7-Field photos
M3F= Modified 3-Field photos

1 Retreatment with steroid injections or laser photocoagulation (if applicable) should be administered at 4-month intervals unless there are specific reasons not to treat in which case the investigator may decide to postpone treatment (see protocol section 4.8.3).
2 Safety visits are performed at Day 4 and Month 1 after each injection.
3 To be performed within 21 days prior to randomization.
4 To be performed within 8 days prior to randomization
5 Examination data to be collected on both eyes.
6 Examination data to be collected on study eye only.
7 Examination data to be collected on the injected eye only.
8 Examination includes both a dilated fundus examination and a slit-lamp examination.
9 To be performed using the modified AREDS lens grading system.
10 OCT measurements will be performed twice on the same day in both eyes. This will occur within 21 days prior to randomization.

Note: Visit windows at M8, M16, M20, M28, M32 may be extended, if necessary, so that the visit occurs no sooner than 3.5 months from the last treatment.