Diabetic Retinopathy Clinical Research Network

Prompt Panretinal Photocoagulation Versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

Version 2.0

October 28, 2014

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CHAPTER 1. BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background and Rationale

1.1.1 Public Health Impact of Diabetic Retinopathy

It is estimated that diabetes mellitus affects 4% of the world's population, almost half of whom have some degree of diabetic retinopathy at any given time. Diabetic retinopathy remains the leading cause of visual loss and new-onset blindness in the United States for those 20 through 74 years of age.[1] The prevalence of diabetic retinopathy in patients with diabetes older than 40 years of age exceeds 40%, with 5% to 10% developing vision-threatening complications, including proliferative diabetic retinopathy (PDR), capillary non-perfusion, or macular edema.[1] Aiello reported that the annual economic impact of retinopathy-associated morbidity in the United States likely exceeds $620 million.[2] Given the aging United States population and the concomitant increasing age-specific prevalence of diabetes, the public health impact of diabetic retinopathy is enormous.[3]

Advancing diabetic retinopathy is characterized by increasing retinal ischemia. The anatomic sequel of this pathophysiologic change, retinal neovascularization or PDR, is a major cause of preventable and potentially irreversible vision loss in patients with diabetes. Data from the Diabetic Retinopathy Study suggest that given long enough duration of diabetes, approximately 60% of patients with diabetes melitus will develop PDR. Without intervention, nearly half of these eyes with PDR will experience profound visual loss (Snellen visual acuity worse than 5/200) from associated complications including vitreous hemorrhage and/or tractional retinal detachment.[4]

1.1.2 Proliferative Diabetic Retinopathy: Impact on Vision Loss, Treatment, and Complications from Treatment

The initial manifestation of PDR is retinal neovascularization at the disc or elsewhere. Vitreous hemorrhage and tractional retinal detachment from PDR are important causes of severe visual loss and new onset blindness in developed countries worldwide. According to Aiello (2005), despite advances in the treatment of both diabetes and diabetic retinopathy, in the United States alone there are approximately 700,000 persons with PDR, with 63,000 new cases of proliferative retinopathy annually. Furthermore, the Centers for Disease Control and Prevention reported in 2007 that there are 12,000-24,000 new cases of diabetic retinopathy-induced blindness each year.[2, 5]

PDR is currently treated with scatter or panretinal photocoagulation (PRP) which destroys areas of retina but preserves central vision. Multicenter clinical trials have demonstrated the effectiveness of PRP in preserving vision and reducing the risk of vision loss.[6, 7] The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that PRP applied when an eye approaches or just reaches high risk PDR reduces the risk of severe vision loss to less than 4%.[8] Subsequent analyses of the ETDRS data revealed that early PRP was also effective in preventing severe visual loss specifically in patients with type 2 diabetes who had severe non-proliferative diabetic retinopathy (NPDR) or early PDR.[9]

In PRP, typically 1200 to 1800 laser burns (approximately 500 µm in size on the retina) are applied to the peripheral retinal tissue, focally destroying outer photoreceptors and retinal

pigment epithelium. Large vessels are avoided, as are areas of pre-retinal hemorrhage. The treatment is thought to exert its effect by increasing oxygen delivery to the inner retina and decreasing viable hypoxic cells which are producing growth factors such as VEGF. The total treatment is usually applied over one to four sessions, spaced one to two weeks apart. Follow-up evaluation usually occurs at one month, and then three to four months after completion of treatment. Response to PRP varies, while it is most desirable to see a regression of new vessels, stabilization of neovascularization with no further growth may also result.

Occasionally, macular edema may develop or pre-existing DME may worsen following PRP.[10, 11] The ETDRS, which was performed prior to OCT availability, found that among eyes with no central retinal thickening at baseline in graded fundus photographs, retinal thickening was present at 4 months in 16% of eyes that underwent full PRP compared with 12% in eyes for which scatter photocoagulation was not performed.[12] Furthermore, in patients with center-involved DME requiring PRP who also receive focal/grid laser, exacerbation of macular edema associated with visual acuity loss has also been documented.[11, 13] Unpublished data from the ETDRS shows that 14% of eyes with some PDR (level 61 or worse) and macular edema with center involvement at initiation of PRP lose at least 10 letters of vision from baseline to 4 months, while 14% also lose at least 15 letters at 4 months (unpublished data from the ETDRS analyzed by Coordinating Center for the DRCR Network).

Although remarkably effective at reducing visual loss if applied in a timely and appropriate manner, PRP treatment destroys viable retinal tissue and is associated with well-documented potential side effects in addition to exacerbation of macular edema that may lead to transient or permanent loss of visual function, including peripheral visual field defects, night vision loss, loss of contrast sensitivity, potential complications from misdirected or excessive burns, and progression of visual loss in nearly 5% of individuals despite appropriate treatment.[14] Because of these side effects, there is interest and rationale, from a public health point of view, for exploring therapeutic alternatives that might delay or obviate the need for this inherently destructive procedure, since PRP-associated vision loss may lead to lost work time, lost wages, decreased ability to care for diabetes, or decreased ability to drive safely.

1.1.3 Rationale for Anti-VEGF Therapy for PDR

Multiple studies have implicated VEGF as a major causative factor in human eye diseases characterized by neovascularization, including PDR. [15-25] Thus, inhibition of VEGF would be expected to reduce PDR.

In 1994, investigators reported significantly increased concentrations of VEGF in ocular fluid samples from patients with active ocular neovascularization from PDR as compared with those with NPDR or quiescent PDR, suggesting that VEGF is a primary mediator of diabetic retinal neovascularization.[17] Since that time, a number of clinical case reports and small series have suggested that anti-VEGF therapy is effective in transiently regressing PDR.[26-31] Several different anti-VEGF drugs exist, including pegaptanib (Macugen, Eyetech Pharmaceuticals), ranibizumab (Lucentis, Genentech, Inc.), bevacizumab (Avastin, Genentech, Inc.) and VEGF Trap (Regeneron, Inc.). Published reports suggest that there is a consistent and rapid response of ocular neovascular disease to anti-VEGF agents as a therapeutic class. A recent publication reported complete resolution of angiographic leakage of neovascularization of the disc due to PDR in 19 of 26 eyes (73%) that were treated with intravitreal bevacizumab.[29] Biologic effects of regression of neovascularization were seen at bevacizumab doses as low as 6.2 µg, which is

200 fold less than the standard clinically used dose of 1.25 mg. Another small prospective, open-label exploratory study randomized 20 subjects with active PDR to treatment with intravitreal pegaptanib versus PRP. By week 12, all pegaptanib-treated eyes demonstrated complete regression of neovascularization, which was maintained through the final study visit at week 36.[32]

As indicated above, the current standard treatment for PDR is PRP, but this treatment is inherently destructive and has several potential adverse effects on aspects of visual function, including constriction of peripheral visual fields and decreases in night vision, contrast sensitivity and color perception. Thus, therapeutic alternatives that might delay or obviate the need for PRP are desirable. It is possible that anti-VEGF treatment could prevent laser-associated vision loss by precluding the need for PRP as long as the eye continued to receive it. Even if anti-VEGF treatment was discontinued and there was an eventual need for PRP due to recurrent, active PDR, it is possible that initial treatment with anti-VEGF therapy might improve visual outcomes substantially by delaying or preventing the need for PRP.

1.1.3.1 Role of Anti-VEGF Treatment in Eyes with PDR + DME

Based on recent trial results from the DRCR.net and other investigative groups,[33-35] eyes with PDR that also have center-involved DME are increasingly likely to receive anti-VEGF therapy as standard care. Results from the DRCR.net Laser-Ranibizumab-Triamcinolone for DME Study (Protocol I) were published in June, 2010, and indicate that treatment for DME with intravitreal ranibizumab plus deferred or prompt focal/grid laser provides visual acuity outcomes at 1 year and 2 years that are superior to focal/grid laser alone.[36] This study enrolled 854 study eyes of 691 study participants with DME involving the fovea and with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320. Eyes were randomized to sham+prompt focal/grid laser (n=293), 0.5-mg ranibizumab+prompt laser (within 3-10 days, n=187), 0.5-mg ranibizumab+deferred laser (deferred for at least 24 weeks, n=188), or 4-mg triamcinolone+prompt laser (n=186). Treatment with ranibizumab was generally continued on a monthly basis unless the patient's vision stabilized or reached 20/20, or the retinal swelling resolved. Treatment could be stopped if failure criteria were met (persistent swelling with substantial visual acuity loss of at least 10 letters from baseline), but this degree of vision loss occurred in very few study participants (less than 5% in any group by 1 year) assigned to ranibizumab. The mean change ($\pm$ standard deviation) in visual acuity letter score at 1 year from baseline was significantly greater in the ranibizumab+prompt laser group (+9 ± 11, P<0.001) and the ranibizumab+deferred laser group (+9 ± 12, P<0.001) as compared with the sham+prompt laser group (+3 ± 13). The one-year OCT results paralleled the visual acuity results. No apparent treatment-related systemic events were observed.

The Protocol I results provided definitive confirmation of the promising role of anti-VEGF therapy suggested by phase 2 trials (DRCR.net Protocol H, READ2, RESOLVE)[33, 34] and recently were confirmed in reports (not yet published) from similarly designed phase III trials (RESTORE, RISE, RIDE), [35, 37-39] that evaluated anti-VEGF therapy for maintaining or improving vision in substantial proportions of patients with central DME and at least some visual acuity impairment. Given the widespread influence of previous DRCR.net studies on United States practice patterns for treatment of DME (e.g., the marked drop in nationwide use of intravitreal steroid for DME after the publication of the Protocol B primary paper[40]), it is expected that the results from Protocol I will similarly influence retina physicians with regard to treatment of center-involved DME, with a corresponding rise in the use of anti-VEGF therapy for DME. Given the high likelihood that beginning this year, eyes with PDR and DME will

receive anti-VEGF therapy as standard care for the DME, it will be valuable to compare visual acuity and visual function outcomes in eyes receiving anti-VEGF for DME that receive prompt versus deferred PRP as well as to assess whether the anti-VEGF treatment obviates the need for PRP over the long-term.

1.1.3.2 Ranibizumab

Ranibizumab, the anti-VEGF drug to be used in this trial, is a humanized monoclonal antibody fragment which binds to and inhibits VEGF in the extracellular space. It is designed to block all isoforms of VEGF-A. It was approved by the FDA as treatment for neovascular age-related macular degeneration in 2006 and approved for treatment of macular edema from branch or central retinal vein occlusions in 2010. Intravitreal ranibizumab in doses up to 2 mg appear to be well tolerated.[41] Although studies of ranibizumab as treatment for PDR have been limited to date likely due to the high cost of the drug, it is known to be highly effective in the treatment of ocular neovascularization associated with age-related macular degeneration.[42] Furthermore, preliminary data from Protocol I reveal that eyes assigned to the ranibizumab treated groups were less likely to have a vitreous hemorrhage or receive PRP than the sham+prompt laser group (3% versus 7%) during the first year of follow up, and less likely to progress from severe NPDR to PDR (8% versus 42%), even though ranibizumab was not given monthly to all study participants following the 12-week visit, suggesting a beneficial effect of ranibizumab treatment on diabetic retinal neovascularization which might not require monthly treatments indefinitely to achieve this beneficial effect.[36]

1.1.4. Summary of Rationale

Current standard treatment for PDR is PRP, but this treatment is inherently destructive and has several potential adverse effects on aspects of visual function, including constriction of peripheral visual fields and decreases in night vision, contrast sensitivity and color perception. Thus, therapeutic alternatives that might delay or obviate the need for PRP are desirable. It has been demonstrated that retinal neovascularization from PDR is highly responsive to anti-VEGF therapy, but it is unclear how long regression of retinal neovascularization is sustained after anti-VEGF therapy is halted. It is possible that intravitreal ranibizumab treatment could prevent laser-associated vision loss by precluding the need for PRP as long as the eye continued to receive ranibizumab. Even if ranibizumab treatment was discontinued, it is possible that initial treatment with anti-VEGF therapy might improve visual outcomes substantially by delaying or preventing the need for PRP, and the infrequent frequency of administration of ranibizumab for DME (median 2 to 3 times in the second year of treatment) after the DME initially has resolved on anti-VEGF therapy suggests that monthly ranibizumab might not be needed to achieve control of PDR.

1.2 Study Objectives and Hypothesis

The primary objective of the protocol is to determine if visual acuity outcomes at 2 years in eyes with PDR that receive anti-VEGF therapy with deferred PRP are non-inferior to those in eyes that receive standard prompt PRP therapy.

Secondary objectives include:

- Comparing other visual function outcomes (including Humphrey visual field testing and study participant self-reports of visual function) in eyes receiving anti-VEGF with deferred PRP with those in eyes receiving prompt PRP.
- Determining percent of eyes not requiring PRP when anti-VEGF is given in the absence of prompt PRP.

- Comparing safety outcomes between treatment groups.
- Comparing associated treatment and follow-up exam costs between treatment groups.

1.3 Study Design and Synopsis of Protocol

A. Study Design

- Phase III, prospective, multi-center randomized clinical trial

B. Major Eligibility Criteria

- Age >=18 years
- Type 1 or type 2 diabetes
- Study eye with
  - PDR for which PRP can be safely deferred for at least 4 weeks in the investigator's judgment.
  - No prior PRP (prior PRP is defined as ≥ 100 burns placed previously outside of the posterior pole)
  - Visual acuity letter score in the study eye ≥ 24 (approximate Snellen equivalent of 20/320 or better)

C. Treatment Groups

Study eyes will be assigned randomly (1:1) to one of the following two groups:

- Prompt panretinal photocoagulation
- Intravitreal 0.5 mg ranibizumab with deferred panretinal photocoagulation

Study participants may have one or two study eyes. Study participants with two study eyes will receive prompt PRP in one eye and ranibizumab with deferred PRP in the other eye. Further details on randomization are located in section 2.4.

For both treatment groups, intravitreal ranibizumab may be given as needed for DME. The treatment regimen for PDR and DME are described in sections 4.2-4.4.

D. Sample Size

- A minimum of 380 eyes (approximately 316 study participants assuming 20% have two study eyes)

E. Duration of Follow-up

- Primary outcome: 2 years
- Total follow-up: 5 years

F. Follow-up Schedule

- Year 1: For eyes assigned to the ranibizumab with deferred PRP group, follow-up visits occur every 4 weeks unless PRP is given (see section 3.1.2). For eyes assigned to the prompt PRP group, follow-up visits occur every 16 weeks. Eyes may be seen more frequently for DME treatment as needed.
- Years 2 and 3: Follow-up visits occur every 4 to 16 weeks depending on disease progression and treatment administered (see section 3.1.2).

- During years 4 and 5: Participants who agree will be followed according to the visit schedule in Years 2 and 3; otherwise, treatment and follow-up is performed as part of the study participant's usual care. All participants will have study visits at 4 and 5 years.

G. Main Efficacy Outcomes

1. Treatment group comparisons:

   Primary: Mean change in visual acuity from baseline to 2 years

   Secondary:

   - Mean visual acuity over two years (area under the curve analysis)
   - Proportion of eyes with 10 and 15 letter vision loss or gain
   - Humphrey visual field (HVF) testing (at sites with HVF capabilities), NEI VFQ-25, and UAB-LLQ
   - Need for supplemental PRP (see section 4.3.2) after completion of deferred or prompt initial PRP
   - Need for vitrectomy (see section 5.2)
   - Mean change in OCT central subfield thickness, other retinal thickness outcomes
   - In eyes without central subfield involved DME at baseline, proportion with progression to central subfield involved DME
   - Percent of eyes with vitreous hemorrhage
   - Proportion with complete regression of neovascularization on fundus photography
   - Associated treatment and follow-up costs

2. Assessment of treatment group receiving anti-VEGF with deferred PRP:
   - Percent not requiring PRP in the deferred PRP group at 2 years

Eyes with and without DME at randomization will be pooled for the primary analysis, however separate exploratory analyses of subgroups based on baseline DME status will be conducted.

Outcome analyses at 2 years will be repeated at years 3, 4, and 5.

H. Main Safety Outcomes

Injection-related: endophthalmitis, tractional retinal detachment, rhegmatogenous retinal detachment, retinal tears, cataract, intraocular hemorrhage

Ocular drug-related: inflammation, cataract, cataract surgery, increased intraocular pressure, new or worsening neovascular glaucoma, glaucoma medications, glaucoma surgery, new or worsening tractional retinal detachment, progression of tractional retinal detachment from extramacular to macular, new or worsening neovascularization of the iris

Systemic drug-related: hypertension, cardiovascular events, cerebrovascular events

I. Schedule of Assessment Visits and Examination Procedures

	0	Treatment Visits Every 4-16w*	Non-Annual Assessment Visits†	Annual Visits
Visit Window		(+/- 1w)	(+/- 2 to 4w)	(+/- 4w)
E-ETDRS best corrected visual acuity[a]	X	X	X	X
Binocular visual acuity[b]	X			X
Ancillary visual field testing[c]	X			X
Questionnaires [d]	X		X	X
OCT [e]	X	X		X
Eye Exam[f]	X	X	X	X
Fundus Photography [g]	X			X
Blood pressure	X			
HbA1c[h]	X			

*= visits every 4 weeks (w) during the first year for eyes assigned to ranibizumab with deferred PRP; if intravitreal ranibizumab treatment is initiated for DME in either group, additional visits for DME treatment may occur every 4 to 16 weeks as needed. After one year from initial ranibizumab treatment for PDR or once PRP is given, visits every 4-16 weeks based on disease progression and treatment administered

†=visits at 16(±2), 32(±2), 68(±4), 84(±4), 120(±4), and 136(±4). For participants who agree to structured follow-up in Years 4 and 5, additional assessment visits at 172(±4), 188(±4), 224(±4), and 240(±4) weeks.

a= both eyes including protocol refraction in the study eye at each visit. Protocol refraction in nonstudy eye is only required at baseline and annual visits. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.

b = binocular vision test using habitual correction on the Electronic Visual Acuity Tester

c=Humphrey visual field testing (30-2 and 60-4 test patterns; at sites with HVF testing capabilities)

d= only in participants with one study eye; includes NEI VFQ-25, UAB LLQ, and TTO annually only; WPAI at 4w and each subsequent assessment visit

e= study eye only at annual visits for all eyes and at each follow-up visit for eyes in which DME treatment is initiated

f=both eyes at baseline; study eye only at each follow-up visit including slit lamp exam, lens assessment, measurement of intraocular pressure, and dilated ophthalmoscopy; examination of the angle required if NVI or increased intraocular pressure present.

g= study eye only at baseline, annual visits AND prior to initiating PRP in the deferred group; 7SF or 4WF with additional fields as necessary to capture presence of neovascularization

h=does not need to be repeated if HbA1c is available from within the prior 3 months. If not available, can be performed within 3 weeks after randomization.

1.4 General Considerations

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

The DRCR.net Procedures Manuals (visual acuity-refraction testing procedures manual, photography procedures manual, OCT procedures manuals, and study-specific procedures manual) provide details of the examination procedures and intravitreal injection procedure.

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

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

CHAPTER 2.
STUDY PARTICIPANT ELIGIBILITY AND ENROLLMENT

2.1 Identifying Eligible Study Participants and Obtaining Informed Consent

A minimum of 380 eyes are expected to be enrolled. Assuming that 20% of the study participants have two study eyes, this equates with an enrollment of about 316 study participants, with a goal to enroll an appropriate representation of minorities. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Study participants who have signed an informed consent form can be randomized up until the end date, which means the recruitment goal might be exceeded.

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

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

Once a study participant is randomized, that participant will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible and will accept assignment to any one of the 2 treatment groups.

2.2 Study Participant Eligibility Criteria

2.2.1 Individual-level Criteria

Inclusion

To be eligible, the following inclusion criteria (1-4) must be met:

1. Age >= 18 years
   - *Individuals <18 years old are not being included because PDR is so rare in this age group that the diagnosis of PDR may be questionable.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes*
     - *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes*

- *Documented diabetes by ADA and/or WHO criteria (see Procedures Manual for definitions)*

3. At least one eye meets the study eye criteria listed in section 2.2.2.
4. Able and willing to provide informed consent.

Exclusion

An individual is not eligible if any of the following exclusion criteria (5-13) are present:

5. Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant.
6. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control).
   - *Individuals in poor glycemic control who, within the last 4 months, initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next 4 months should not be enrolled.*
7. Participation in an investigational trial within 30 days of randomization that involved treatment with any drug that has not received regulatory approval for the indication being studied.
   - *Note: study participants cannot receive another investigational drug while participating in the study.*
8. Known allergy to any component of the study drug.
9. Blood pressure > 180/110 (systolic above 180 or diastolic above 110).
   - *If blood pressure is brought below 180/110 by anti-hypertensive treatment, individual can become eligible.*
10. Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 4 months prior to randomization.
11. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.
    - *These drugs should not be used during the study.*
12. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 3 years.
    - *Women who are potential study participants should be questioned about the potential for pregnancy. Investigator judgment is used to determine when a pregnancy test is needed.*
13. Individual is expecting to move out of the area of the clinical center to an area not covered by another DRCR.net certified clinical center during the 3 years of the study.

2.2.2 Study Eye Criteria

The potential study participant must have at least one eye meeting all of the inclusion criteria (a-c) and none of the exclusion criteria (d-p) listed below.

A study participant can have two study eyes only if both are eligible at the time of randomization. For study participants with two eligible eyes, the logistical complexities of the protocol must be considered for each individual prior to randomizing both eyes.

The eligibility criteria for a study eye are as follows:

Inclusion

a) Presence of PDR which the investigator intends to manage with PRP alone but for which PRP can be deferred for at least 4 weeks in the setting of intravitreal ranibizumab, in the investigator's judgment.

b) Best corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity letter score ≥ 24 (approximate Snellen equivalent 20/320) on the day of randomization.

c) Media clarity, pupillary dilation, and study participant cooperation sufficient to administer PRP and obtain adequate fundus photographs and OCT.

- *Investigator must verify accuracy of OCT scan by ensuring it is centered and of adequate quality*

Exclusion

The following exclusions apply to the study eye only (i.e., they may be present for the nonstudy eye):

d) History of prior panretinal photocoagulation (prior PRP is defined as ≥100 burns outside of the posterior pole)

e) Tractional retinal detachment involving the macula.

- *A tractional retinal detachment is not an exclusion if it is outside of the posterior pole (not threatening the macula) and in the investigator's judgment, is not a contraindication to intravitreal ranibizumab treatment and also does not preclude deferring PRP for at least 4 weeks in the setting of intravitreal ranibizumab*

f) Exam evidence of neovascularization of the angle (neovascularization of the iris alone is not an exclusion if it does not preclude deferring PRP for at least 4 weeks in the investigator's judgment).

g) If macular edema is present, it is considered to be primarily due to a cause other than diabetic macular edema.

- *An eye should not be considered eligible if: (1) macular edema is present that is considered to be related to ocular surgery such as cataract extraction or (2) clinical exam and/or OCT suggest that vitreoretinal interface abnormalities disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of any macular edema.*

h) An ocular condition is present (other than diabetic retinopathy) that, in the opinion of the investigator, might alter visual acuity during the course of the study (e.g., retinal vein or artery occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.).

- *A vitreous or preretinal hemorrhage is not an exclusion if it is out of the visual axis and in the investigator's judgment is not having any affect on visual acuity.*

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

j) History of intravitreal anti-VEGF treatment at any time in the past 2 months.

k) History of corticosteroid treatment (intravitreal or peribulbar) at any time in the past 4 months.

- *If the investigator believes that there may still be a substantial effect 4 months after prior treatment (e.g., dose of intravitreal triamcinolone higher than 4 mg), the eye should <u>not</u> be included.*

l) History of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months following randomization.

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

n) Aphakia.

o) Uncontrolled glaucoma (in investigator's judgment).

p) Exam evidence of severe external ocular infection, including conjunctivitis, chalazion, or substantial blepharitis.

2.3 Screening Evaluation and Baseline Testing

2.3.1 Historical Information

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

2.3.2 Baseline Testing Procedures

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

- If a procedure has been performed (using the study technique and by study certified personnel) as part of usual care, it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.
- The testing procedures are detailed in the DRCR.net Procedures Manuals (visual acuity-refraction testing procedures manual, photography procedures manual, OCT procedures manuals, and study-specific procedures manual). Visual acuity testing, ocular exam, fundus photography, and OCT are to be performed by DRCR.net certified personnel.
- The fundus photographs will be sent to a fundus photograph reading center for grading but study participant eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation).
- OCTs meeting DRCR.net criteria for manual grading will be sent to the reading center but assessment for treatment of DME is determined by the site (i.e., individuals deemed to have center-involved DME by the investigator can be treated with ranibizumab for DME without pre-treatment reading center confirmation).

1. E-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye. *(on day of randomization)*
2. Binocular E-ETDRS visual acuity testing with the participant's habitual correction ("everyday" glasses or contacts) using the Electronic Visual Acuity Tester. *(on day of randomization following OD/OS testing)*

3. Humphrey visual field testing using 30-2 and 60-4 test patterns; if site has the capability. *(within 14 days prior to randomization)*

4. Questionnaires. *(only in participants with one study eye; within 14 days prior to randomization)*

    - NEI Visual Functioning Questionnaire-25 *(NEI-VFQ; measures the dimensions of self-reported vision-targeted health status that are most important for individuals who have chronic eye diseases),*

    - UAB Low Luminance Questionnaire *(UAB-LLQ; a 32-item questionnaire designed to assess self-reported visual problems under low luminance and at night for use in studies on age-related maculopathy)*

    - Time Trade-Off Questionnaire *(TTO; rating-scale technique used to calculate quality-adjusted life years); not required for randomization.*

    - Workplace Productivity and Activity Impairment Questionnaire *(WPAI; a 6-item questionnaire that collects data on employment and whether vision problems are thought to affect productivity); not required for randomization.*

5. OCT in the study eye on DRCR.net-approved time domain or spectral domain OCT machine. *(within 8 days prior to randomization)*

    - *Investigator must verify accuracy of OCT scan by ensuring it is centered and of adequate quality*

6. Ocular examination of each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy on the study eye; examination of the angle is required if neovascularization of the iris is present or increased intraocular pressure (IOP) defined as ≥30 mm Hg *(on day of randomization)*

7. ETDRS protocol 7 standard-field or 4 wide-field digital stereoscopic fundus photography in the study eye; if neovascularization is not captured on the standard photographs, additional fields should be taken as necessary to confirm presence of PDR (*within 21 days prior to randomization)*

8. Measurement of blood pressure

9. Laboratory testing- Hemoglobin A1c
    - *HbA1c does not need to be repeated if available in the prior 3 months. If not available at the time of randomization, the potential study participant may be enrolled but the test must be obtained within 3 weeks after randomization.*

2.4 Enrollment/Randomization of Eligible Study participants

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

2. The baseline treatment (injection and/or PRP according to treatment group assignment and presence of DME) must be initiated on the day of randomization; therefore, a study participant should not be randomized until this is possible. For study participants with two study eyes that will be treated with ranibizumab at baseline, both eyes may be injected on the same day or on separate days as long as the second eye is injected within one week of randomization.

3. Randomization is completed on the DRCR.net website.

- Study participants with one study eye will be randomly assigned (stratified by site and presence or absence of central involved DME) with equal probability to one of the treatment groups:
    - Group A: Prompt PRP
    - Group B: 0.5 mg ranibizumab with deferred PRP

- For study participants with two study eyes (both eyes eligible at the time of randomization),
    - The study participant will be randomized with equal probability to receive either:
        - Group A in the eye with greater OCT central subfield and Group B in the eye with lower OCT central subfield
        - Group B in the eye with greater OCT central subfield and Group A in the eye with lower OCT central subfield

  Note: if both eyes have the same OCT central subfield, the right eye will be considered the eye with the greater OCT central subfield.

Presence of DME will be defined on OCT central subfield as ≥ 250 microns on Zeiss Stratus OCT (or equivalent thickness on spectral domain OCT machine).

CHAPTER 3.
FOLLOW-UP VISITS AND TESTING

3.1 Visit Schedule

3.1.1 Assessment Visits

The schedule of protocol-specified assessment visits is as follows (additional treatment visits may be required as indicated below):

Year 1

- Visits at 16, 32, 52 (±2 weeks)

Years 2 and 3

- Visits at 68, 84, 104, 120, 136, and 156 weeks (±4 weeks)

Years 4 and 5

- For participants who agree, visits at 172, 188, 224, and 240 weeks (±4 weeks)
- Visits at 208 and 260 weeks (±8 weeks) for all participants.

3.1.2 Treatment Visits for PDR

For eyes assigned to ranibizumab plus deferred PRP, the study participant will have more frequent visits for treatment. The schedule of protocol-specified treatments visits for the ranibizumab plus deferred PRP group is as follows:

Year 1

- Prior to treatment with PRP: visits every 4±1 weeks in between assessment visits (with a minimum of 21 days between visits)
- If PRP is given: visits every 4±1 weeks (with a minimum of 21 days between visits) as long as intravitreal injections are given; otherwise, visits every 4 to 16 weeks (±1 week windows)
  - *The first two times an injection is deferred, the study participant will return in 4 weeks for re-evaluation. If deferral continues, the study participant will return in 8 weeks for re-evaluation before beginning the every 16 week schedule.*

Years 2 and 3

- Visits every 4±1 weeks (with a minimum of 21 days between visits) as long as intravitreal injections are given
- Otherwise, visits every 4 to 16 weeks (±1 week windows)
  - *The first two times an injection is deferred, the study participant will return in 4 weeks for re-evaluation. If deferral continues, the study participant will return in 8 weeks for re-evaluation before beginning the every 16 week schedule.*
- Study treatment discontinued at 3 years

Years 4 and 5

- Participants who agree will be followed according to the visit schedule in Years 2 and 3 above. Otherwise, treatment and follow-up is at investigator discretion (as part of usual care).

3.1.2 Treatment Visits for DME

If intravitreal ranibizumab treatment for DME is warranted, follow-up visits for treatment may occur every 4 to 16 weeks at the discretion of the investigator. Criteria for initiating DME treatment and guidelines for retreatment and follow-up are provided in section 4.4.

3.2 Testing Procedures

The following procedures will be performed at each protocol visit on the study eye only unless otherwise specified. A grid in section 1.3 summarizes the testing performed at each visit. Visual acuity testers and OCT technicians will be masked to treatment group at annual visits.

1. E-ETDRS visual acuity testing in each eye (best corrected).
   - A protocol refraction in the study eye is required at all protocol visits. Refraction in the non-study eye is only required at annual visits. When a refraction is not performed, the most-recently performed refraction is used for the testing.
2. Binocular E-ETDRS visual acuity testing using the participant's habitual correction ("everyday" glasses or contacts)
3. Humphrey visual field testing (30-2 and 60-4 test patterns; if site has HVF testing capabilities) at annual visits.
4. Questionnaires (only in participants with one study eye).
   - Includes NEI-VFQ 24, UAB-LLQ, and TTO (for willing participants) at annual visits only; WPAI (for willing participants) at 4 weeks and each subsequent "assessment visit"
5. OCT on the study eye at annual visits and DME treatment visits.
   - If visual acuity has decreased by 10 letters (2 lines) since the last visit in an eye with no prior treatment for DME during the study, an OCT should be performed to determine if DME is the cause of vision loss.
   - If DME treatment will be initiated, an OCT must be done prior to performing the first ranibizumab injection.
6. Ocular exam on the study eye at each visit, including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy; undilated exam of the iris is at the discretion of the investigator; examination of the angle is required if neovascularization of the iris is present or increased IOP (defined as one of the following: a) IOP $\geq$ 30mm Hg b) first time IOP has increased at least 10mm Hg since baseline c) IOP has increased at least 10mm Hg since last visit or d) IOP lowering medication initiated since last visit).
7. Fundus photographs on the study eye (7 standard-field or 4 wide-field digital stereoscopic) at annual visits and prior to initiating PRP in the deferred group; if additional fields were taken at baseline to capture the neovascularization, the same fields should be taken for each set of follow-up photographs.

All of the testing procedures do not need to be performed on the same day, provided that they are completed within the time window of a visit and prior to initiating any retreatment.

Testing procedures at unspecified visits are at investigator discretion. However, it is recommended that procedures that are performed should follow the standard DRCR.net protocol for each procedure.

CHAPTER 4.
TREATMENT REGIMEN

4.1 Introduction

All study eyes will be randomly assigned to one of the following two treatment groups:

- A: Prompt PRP
- B: 0.5mg ranibizumab with deferred PRP

For both treatment groups, study intravitreal ranibizumab must be given at baseline if OCT central subfield thickness is ≥250 microns on Zeiss Stratus (or or equivalent thickness on spectral domain OCT machine) and visual acuity is ≤78 (20/32 or worse). Study intravitreal ranibizumab may be given for DME that develops during follow-up at the discretion of the investigator (non-study anti-VEGF drugs or alternative treatments for DME should not be given).

Eyes assigned to ranibizumab with deferred PRP or with DME present at baseline will be given the initial injection on the day of randomization. For study participants with two study eyes that will be treated with ranibizumab, both eyes may be injected on the day of randomization or on separate days. If the injections will occur on separate days, the second eye must be injected within one week of the first injection given on the day of randomization.

Eyes assigned to the prompt PRP group will receive panretinal photocoagulation, which is initiated on the day of randomization for eyes without DME or initiated within 0 to 14 days of baseline injection if DME is present at baseline for which intravitreal ranibizumab is indicated (if performed on the same day, PRP must be performed prior to injection).

The timing and criteria for retreatment for PDR and DME with ranibizumab and assessment for PRP in the deferred PRP group are detailed in sections 4.2-4.4 below. Treatment procedures are described in sections 4.5-4.7.

4.2 Intravitreal Injection Treatment for PDR During Follow Up in the Ranibizumab with Deferred PRP Group

See section 4.5 for details regarding the study drug and injection procedure.

4.2.1 Intravitreal Injection at 4-week, 8-week and 12-week Follow-up Visits

All study eyes randomized to receive ranibizumab with deferred PRP will receive an injection for PDR at the 4, 8, and 12 week visit. If an eye experienced adverse effects from a prior intravitreal injection, retreatment with intravitreal ranibizumab is at the discretion of the investigator.

4.2.2 Intravitreal Injection at and after the 16-week Follow-up Visit

Starting at the 16-week visit, study eyes randomized to receive ranibizumab with deferred PRP will be evaluated for retreatment with intravitreal injection for PDR based on appearance of neovascularization.

If an eye has experienced adverse effects from prior intravitreal injection treatment, retreatment with intravitreal ranibizumab is at the discretion of the investigator. In addition, if any future treatment with ranibizumab is contraindicated based on a previous adverse reaction, treatment

with PRP for PDR is at investigator discretion after discussion with and approval from the Protocol Chair or Coordinating Center designee. Each eye with no contraindication to additional injections will be categorized into one of the following 5 categories based on neovascularization (NV) status:

** Note: examination of the angle is required if NV of the iris or increased IOP (see definition in section 3.2) is present ; otherwise it is at investigator discretion; however, if the angle is examined, then the results from this examination should be factored into the subsequent treatment decision.*

- **Resolved**
  - NV (of the retina, disc, AND iris/angle*) is absent and visualization of the entire retina is adequate to completely assess for NV. Decision to re-inject is at investigator discretion. In general, if NV is completely regressed the injection should be deferred. PRP should not be given.

- **Improved**

  NV (of the retina, disc OR iris/angle*) still persists, but there is evidence of improvement (improvement defined as a decrease in the size of NV or diminished density of NV) since the last visit and visualization of the entire retina is adequate to completely assess for NV. An injection is given. PRP should not be given.

- **Stable**
  - NV (of the retina, disc AND iris/angle*) is clinically unchanged since the last visit and visualization of the entire retina is adequate to completely assess for NV. Once the eye meets criteria for stability, at least 2 more injections must be given, each one month apart (one at the visit at which stability criteria are met and the second at the following study visit one month later if still stable). Further reinjection is then at investigator discretion as long as the eye remains stable. PRP should not be given.

- **Not fully treated**
  - Failure/futility criteria not met and recurrent or worsening NV (of the retina, disc *OR* iris) is present since the last visit in an eye that has had fewer than 4 injections over the previous 4 months or there is vitreous or preretinal hemorrhage preventing adequate visualization of the fundus to assess NV status. An injection is given. PRP should not be given.

- **Failed/futile**
  - Failure/futility criteria met. Decision to re-inject is at investigator discretion. PRP may be given at this time (see below for cases that first require discussion with the Protocol Chair or Coordinating Center designee), in which case the eye will be considered a failure for analyses using PRP as an outcome.

    - *Failure criteria are defined as*
      1. *growth of NV or new NV of the retina, disc OR iris since the last visit such that the NV, including fibrosis, is greater in extent than*

at baseline and at least 4 study injections have been given over the previous 4 months. The investigator may perform PRP.

OR

2. *New or worsened NV of the angle* has developed since the last visit. The investigator may perform PRP.*

OR

3. *definite worsening of NV or fibrous proliferation of the retina, disc OR iris at least 1 day after the last injection that the investigator believes is likely to lead to substantial vision loss if PRP is not performed within 1 week. PRP may only be performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.*

- *Futility criteria are defined as continued persistence or recurrence of NV at 1.5 years or later follow-up that is equal to or greater than the extent of the NV present at baseline and at least 5 study injections performed over the preceding 6 months. PRP may only be performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.*

4.2.3 Next Retreatment Evaluation

Follow-up visits to evaluate for PDR retreatment are every 4 weeks in the first year as long as the eye has not received PRP. At and after 52 weeks or once PRP is given in the first year, if the injection for PDR is deferred at the current and previous 2 visits, the next study follow-up visit is in twice the time since the last visit up to a maximum of 16 weeks between visits. Otherwise, next study follow-up visit is in 4 weeks.

4.3 Panretinal Photocoagulation Treatment During Follow-up

Prompt PRP Group

All eyes assigned to the prompt PRP group will receive PRP, which is initiated on the day of randomization for eyes without DME or initiated within 14 days of baseline injection if DME present at baseline for which intravitreal ranibizumab is indicated (if performed on the same day, PRP must be performed prior to injection). The full session of 1200 to 1600 burns using 500 µm burns on the retina or the equivalent area treated when using indirect laser delivery systems or laser (e.g., Pascal which deliver an automated pattern) must be completed within 56 days of randomization. See section 4.6 for details regarding PRP procedure.

Alternative treatment (e.g. anti-VEGF) for PDR is only permitted in this group if neovascular glaucoma has developed following completion of PRP. Otherwise, alternative treatment may only be performed after discussion with and approval from the Protocol Chair or Coordinating Center designee.

Ranibizumab Plus Deferred PRP Group

Eyes assigned to ranibizumab with deferred PRP may receive PRP only if failure/futility criteria for intravitreal injection for PDR are met (see Section 4.2.2). Failure criteria for PDR could be

met starting after the first injection. If the investigator believes PRP is warranted prior to meeting failure/futility criteria for PDR, the Protocol Chair or Coordinating Center designee must be contacted for approval. See section 4.6 for details regarding PRP procedure. Once PRP is given in the deferred group, further treatment for PDR is at investigator discretion.

4.3.1 Deferral of Additional Scatter Photocoagulation for Decreased Visual Acuity from Exacerbation of Macular Edema

Before the completion of each PRP sitting, visual acuity testing should be completed using usual care methods. If the usual care visual acuity is decreased from baseline acuity by 10 or more letters (2 or more lines), a study protocol refraction and E-ETDRS best corrected visual acuity should be completed (unless the decrease is due to vitreous hemorrhage). An OCT is to be performed if the E-ETDRS best corrected visual acuity is decreased from baseline acuity by 10 or more letters.

Dilated ophthalmoscopic examination should be carried out to determine that the decreasing vision is not secondary to vitreous hemorrhage. If vitreous hemorrhage is the cause of decreased vision, appropriate scatter therapy for proliferative diabetic retinopathy should continue. If proliferative diabetic retinopathy and vitreous hemorrhage are not responsible for the decreased vision, PRP still should be carried out whenever possible. However, if the investigator believes that exacerbation of macular edema is the cause of the decreased vision, at the investigator's discretion, additional scatter photocoagulation can be deferred for two weeks.

If treatment is deferred because of exacerbation of macular edema, a two-week follow up visit should be scheduled. Visual acuity (with study protocol refraction if 10 or more letters worse than baseline) and OCT are repeated. Continuation of the scatter photocoagulation should be considered and in general is appropriate even if there is a decrease in visual acuity. However, if the visual acuity remains decreased by 10 or more letters and this decrease is secondary to macular edema, the investigator may again defer completion of scatter treatment for an additional two weeks and repeat the process again.

4.3.2 Additional Scatter Photocoagulation for Proliferative Diabetic Retinopathy

If the size or amount of neovascularization increases following completion of the initial PRP session, additional scatter photocoagulation can be given. Scatter photocoagulation can be augmented by “fill-in” scatter between existing burns. In cases in which there is a new vitreous hemorrhage, supplemental scatter treatment should only be given if the size/extent of the retinal neovascularization has increased.

4.4 Treatment for Diabetic Macular Edema

This section describes use of study intravitreal ranibizumab and or focal/grid laser to treat concurrent DME, when indicated, during structured follow-up. Non-study anti-VEGF drugs or alternative treatments (e.g. corticosteroids) are not to be used to treat DME unless otherwise indicated below. Participants who do not agree to structured follow-up during Years 4 and 5, will be treated for DME as part of usual care, without the use of study drug.

If central subfield-involved DME is present at baseline on OCT (central subfield thickness ≥250 microns on Zeiss Stratus or equivalent thickness on spectral domain OCT machine, within 8 days of randomization) and visual acuity is ≤78 (20/32 or worse), intravitreal ranibizumab must be given.

In all other circumstances, treatment with intravitreal ranibizumab and/or focal/grid laser for DME is at investigator discretion. However, if central-involved DME is not present at baseline and develops during follow-up on OCT (central subfield thickness ≥250 microns on Zeiss Stratus or equivalent thickness on spectral domain OCT machine) and the central subfield thickness has increased from baseline at least 25 microns, it is recommended that intravitreal ranibizumab be given.

If treatment for DME is warranted, guidelines for intravitreal ranibizumab retreatment are described in section 4.4.1 and for focal/grid photocoagulation in section 4.4.2. See section 4.5 for details regarding study drug and injection procedure. See section 4.7 for details regarding focal/grid photocoagulation procedure.

4.4.1 Intravitreal Injection Retreatment Guidelines for DME

If intravitreal ranibizumab is initiated for DME, the following guidelines are recommended for retreatment. Non-study anti-VEGF drugs and alternative treatment for DME (e.g. corticosteroids) are not permitted unless a minimum of 6 injections have been given and the failure criteria below (#3) are met or Protocol Chair or Coordinating Center designee approval is obtained.

Once intravitreal ranibizumab is initiated for DME, it is recommended that the study eye receive a series of study ranibizumab injections 4 weeks apart for 12 weeks (if the eye has already received 4 consecutive injections for PDR over the course of the previous 4 months, this may be skipped or reduced to total 4 consecutive injections).

At the next two 4-week interval visits, the eye may be evaluated for intravitreal injection retreatment based on visual acuity and central subfield thickness on OCT.

Note: all OCT values referenced below are on Zeiss Stratus; spectral domain equivalent may be used.

Each eye with no contraindication to additional injections may be categorized into one of the following 2 categories:

- If the visual acuity letter score is ≥84 (20/20 or better) or the OCT central subfield thickness is <250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), the decision to reinject is at investigator discretion. If an injection is not given, treatment for DME other than focal/grid photocoagulation cannot be given. In general, if both the visual acuity letter score is ≥ 84 and OCT central subfield thickness is <250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), the injection should be deferred.
- If the visual acuity letter score is <84 (worse than 20/20) and OCT central subfield thickness ≥250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), an injection should be given.

At and after approximately 24 weeks from the initial study ranibizumab injection for DME, each eye with no contraindication to additional injections may be categorized into one of the following 4 categories:

1) *Visual acuity letter score ≥84 (20/20 or better) or OCT central subfield thickness <250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine):*
   - Decision to reinject is at investigator discretion. If an injection is not given, treatment for DME other than focal/grid photocoagulation cannot be given. In general, if both the visual acuity letter score is ≥84 and OCT central subfield thickness is <250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), the injection should be deferred.

2) *Visual acuity score <84 (worse than 20/20), OCT central subfield thickness ≥250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), and evidence of improvement since the last injection:*

   Improvement is defined as either OCT central subfield thickness decreased by 10% or more OR visual acuity letter score has improved 5 or more.
   - An injection should be given.

3) *Failure/Futility Criteria Met*

   Failure/futility is defined as: VA letter score <84, OCT CSF ≥250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), DME present on clinical exam that is the cause of the visual loss, complete laser has been given

   AND

   No improvement since the visit at which (or following which) the last laser treatment was given, defined as OCT central subfield thickness decreased by <10% (or increased) AND visual acuity letter score improved by <5 letters [or worsened)

   AND

   Either 1) VA 10 or more worse than the initial study ranibizumab injection and ≥13 weeks since last laser treatment OR 2) ≥ 1 year since first study injection for DME and 29 weeks since last laser:
   - The eye can be treated for DME at investigator discretion. Non-study anti-VEGF drugs or alternative treatments may be given if the eye has already received at least 6 study ranibizumab injections. If feasible, Protocol Chair or Coordinating Center designate approval should be obtained before administering a treatment that has not been FDA approved for DME.

4) *Visual acuity score <84 (worse than 20/20), OCT central subfield thickness ≥250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), failure/futility criteria (see #3) not met, and no improvement since the last injection*:

   No improvement is defined as OCT central subfield thickness not decreased by at least 10% AND visual acuity letter score not improved by at least 5.
   - Decision to reinject is at investigator discretion. In general, it is expected that an injection will be given if there is edema to treat. If an injection is not given, treatment for DME other than focal/grid photocoagulation cannot be given.

4.4.2 Focal/Grid Photocoagulation Treatment for DME during Follow-Up

Focal/grid photocoagulation may be given in lieu of intravitreal ranibizumab if DME develops during follow-up for which the investigator believes intravitreal ranibizumab is not indicated.

If intravitreal ranibizumab is given at baseline or judged indicated during follow-up, it is recommended that no focal/grid photocoagulation be given prior to 24 weeks from initial ranibizumab injection for DME. After 24 weeks of intravitreal ranibizumab treatment, if the OCT central subfield thickness has decreased by less than 10% (or has increased) and visual acuity letter score has improved by less than 5 (or has worsened) from the last 2 consecutive injections and between the last 2 consecutive injections, and the investigator believes that macular edema is present for which focal photocoagulation is indicated, it is recommended that the eye receive focal/grid photocoagulation.

Once focal/grid photocoagulation has been performed during the study, it is recommended that focal/grid photocoagulation be given within 10 days following each intravitreal injection for DME (or at the time of the visit if an injection is not given) unless one of the following is present at the time of the injection:

- Focal/grid laser given in the previous 13 weeks
- Complete focal/grid laser has already been given in the investigator's judgment. Both of the following criteria must be met to be considered "complete" laser:
    - All leaking microaneurysms within areas of retinal thickening or contributing to the edema that is threatening the center of the macula have been directly treated at some time with laser burns directly over the microaneurysms
    - All other areas of current retinal thickening have been treated with laser burns (either focal or grid), such that the laser burns are "on average" within 100 microns of each other (range between 50 and 150 microns) in a grid pattern throughout the area of retinal thickening
- The central subfield thickness is <250 microns and there is no edema threatening the fovea (i.e., edema within 500 microns of the foveal center, or edema associated with lipid within 500 microns of the foveal center or 1 disc area of edema within 1 disc area of the foveal center).

4.4.3 Next Retreatment Evaluation

Follow-up visits for DME treatment may occur at 4, 8, or 16-week intervals, as needed. It is recommended that follow-up visits occur every 4 weeks for the first year from initial ranibizumab treatment for DME. After the first year, if the injection is deferred for both DME treatment and PDR treatment (see Section 4.2) at the current and previous 2 visits, the next study follow-up visit is recommended in twice the time since the last visit up to a maximum of 16 weeks between visits. Otherwise, the next study follow-up visit should be in 4 weeks.

4.5 Ranibizumab (Lucentis™)

Ranibizumab (Lucentis™) is made by Genentech, Inc. and is approved by the FDA for the treatment of age-related macular degeneration and macular edema secondary to retinal vein occlusion, and approved by the European Medicines Agency and other regulatory authorities outside of the United States for DME.

Study eyes assigned to receive ranibizumab will receive a dose of 0.5mg in 0.05cc. The physical, chemical, and pharmaceutical properties and formulation of ranibizumab are provided in the Clinical Investigator's Brochure.

4.5.1 Intravitreal Injection Technique

The injection is preceded by a povidone iodine prep of the conjunctiva. Antibiotics in the pre-, peri-, or post-injection period are not necessary but can be used at investigator discretion if such use is part of his/her usual routine.

The injection will be performed using sterile technique. The full injection procedure is described in the protocol-specific study procedures manual.

4.5.2 Deferral of Injections Due to Pregnancy

Female study participants must be questioned regarding the possibility of pregnancy prior to each injection. In the event of pregnancy, study injections must be discontinued.

4.5.3 Delay in Giving Injections

If a scheduled injection is not given by the end of the visit window, it can still be given up to 1 week prior to the next visit window opening. If it is not given by that time, it will be considered missed.

If an injection is given late, the next scheduled injection should occur no sooner than 3 weeks (21 days) after the previous injection.

4.6 Panretinal Photocoagulation Technique

Study eyes that receive panretinal photocoagulation (prompt PRP eyes at baseline or deferred PRP eyes that meet failure/futility criteria detailed in section 4.2.2) should have 1200 to1600 burns with a spot size on the retina of approximately 500 microns (or the equivalent area treated with a PASCAL) given over 1 to 3 sittings and completed within 8 weeks (56) days of initiation.

The burn characteristics for non-automated photocoagulation will be as follows:

Size (on retina)	500 microns [e.g. argon laser using 200 micron spot size with Rodenstock lens (or equivalent) or 500 micron spot size with 3 mirror contact lens]
Exposure	0.1 seconds recommended, 0.05 to 0.2 allowed
Intensity	mild white (i.e. 2+ to 3+ burns)
Distribution	edges 1 burn width apart
No. of Sessions/Sittings	1 to 3
Nasal proximity to disk	No closer than 500 microns
Temp. proximity to center	No closer than 3000 microns
Superior/inferior limit	No further posterior than 1 burn within the temporal arcades
Extent	Arcades (~3000 microns from the macular center) to at least the equator
Total # of burns	1200 to 1600: *There may be instances where 1200 burns are not possible such as development of vitreous hemorrhage or study*

	participant inability to complete a sitting precluding completion of the PRP session. Similarly, there may be clinical situations in which more than 1600 burns are needed such as initial difficulty with laser uptake due to media opacity.
Wavelength	Green or yellow (red can be used if vitreous hemorrhage is present precluding use of green or yellow)

An anesthetic injection (retrobulbar, peribulbar or sub-Tenon's) can be used at investigator discretion.

An indirect laser approach can be used at investigator discretion.

If a laser is used that has the capability of producing an automated pattern (e.g. the PASCAL), the automated pattern producing mode is permissible. Guidelines for use of the automated pattern are included in the study procedure manual.

4.7 Focal/Grid Photocoagulation Technique

If focal/grid photocoagulation is warranted, the laser treatment 'session' should generally be completed in a single 'sitting'. The photocoagulation treatment technique, as described below, is a modification of the ETDRS technique and is the treatment approach that is commonly used in clinical practice. Use of fluorescein angiography to direct the treatment is at the discretion of the investigator. Laser treatment following an injection, if needed, will be based on the pre-injection macular appearance.

Burn Characteristic	**Focal/Grid Photocoagulation (non-PASCAL guidelines)* (DRCR.net focal/grid laser technique)**
Direct Treatment	Directly treat all leaking microaneurysms in areas of retinal thickening between 500 and 3000 microns from the center of the macula (although may treat between 300 and 500 microns of macula if central-involved edema persists after initial focal photocoagulation, but generally not if the visual acuity is better than 20/40)
Change in MA Color with Direct Treatment	Not required, but at least a mild gray-white burn should be evident beneath all microaneurysms
Spot Size for Direct Treatment	50 microns
Burn Duration for Direct Treatment	0.05 to 0.1 sec
Grid Treatment	Applied to all areas with edema not associated with microaneurysms. If fluorescein angiography is obtained, grid is applied to areas of edema with angiographic nonperfusion when judged indicated by the investigator.
Area Considered for Grid Treatment	500 to 3000 microns superiorly, nasally and inferiorly from center of macula 500 to 3500 microns temporally from macular center No burns placed within 500 microns of disc
Burn Size for Grid Treatment	50 microns
Burn Duration for Grid Treatment	0.05 to 0.1 sec

Burn Intensity for Grid Treatment	Barely visible (light gray)
Burn Separation for Grid Treatment	2 visible burn widths apart
Wavelength (Grid and Direct Treatment)	Green to yellow wavelengths

**Additional guidelines for performing laser treatment using the PASCAL are included in the Procedure Manual.*

Note:

- *The investigator may choose any laser wavelength for photocoagulation within the green to yellow spectrum. The wavelength used will be recorded.*
- *Lenses used for the laser treatment cannot increase or reduce the burn size by more than 10%. The study procedure manual contains a listing of acceptable lenses.*

CHAPTER 5.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

5.1 Endophthalmitis

Diagnosis and treatment of endophthalmitis is based on investigator's judgment. Obtaining cultures of vitreous and aqueous fluid is highly recommended prior to initiating antibiotic treatment for presumed endophthalmitis.

5.2 Surgery for Vitreous Hemorrhage, Traction Detachment, and Other Complications of Diabetic Retinopathy

A study eye could develop a vitreous hemorrhage or traction detachment that may cause visual impairment. In these cases, vitrectomy may be performed at the discretion of the investigator; however, vitrectomy for hemorrhage alone should not be scheduled for at least 8 weeks after onset of hemorrhage without first discussing with the Protocol Chair or Coordinating Center designee.

5.3 Treatment of Macular Edema in Nonstudy Eye

Treatment of DME in the nonstudy eye is at investigator discretion.

5.4 Diabetes Management

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

5.5 Study Participant Withdrawal and Losses to Follow-up

A study participant has the right to withdraw from the study at any time. If s/he is considering withdrawal from the study, the principal investigator should personally speak to the individual about the reasons, and every effort should be made to accommodate the study participant to allow continued participation if possible.

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

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

Study participants who withdraw or are determined to have been ineligible post-randomization will not be replaced.

5.6 Discontinuation of Study

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

5.7 Contact Information Provided to the Coordinating Center

The Coordinating Center will be provided with contact information for each study participant.

Permission to obtain such information will be included in the Informed Consent Form. The contact information may be maintained in a secure database and will be maintained separately from the study data.

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

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

5.8 Study Participant Reimbursement

The study will be paying the study participant $50 for baseline and each completed annual protocol visit and $25 per completed non-annual protocol visit to cover travel and other visit-related expenses. Payment will be made from the Coordinating Center. Additional travel expenses will be paid in select cases for study participants with higher expenses.

CHAPTER 6.
ADVERSE EVENTS

6.1 Definition

An adverse event is any untoward medical occurrence in a study participant, irrespective of whether or not the event is considered treatment-related. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal lab finding), symptom or disease temporally associated with the use of the treatment, whether or not related to the treatment. This includes preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character.

6.2 Recording of Adverse Events

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

All adverse events whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on an adverse event form online. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

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

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes
There is a plausible temporal relationship between the onset of the adverse event and administration of the study treatment, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study treatment; and/or the adverse event abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the adverse event has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study treatment administration (e.g., cancer diagnosed 2 days after first dose of study drug).

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

Adverse events will be coded using the MedDRA dictionary.

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

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

6.3 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening)
- Is a congenital anomaly/birth defect
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

6.4 Data and Safety Monitoring Committee Review of Adverse Events

A Data and Safety Monitoring Committee (DSMC) will advise the Coordinating Center regarding the protocol, template informed consent form, and substantive amendments and will provide independent monitoring of adverse events. Cumulative adverse event data are semi-annually tabulated for review by the DSMC. Following each DSMC data review, a summary will be provided to institutional review boards. A list of specific adverse events to be reported to the DSMC expeditiously, if applicable, will be compiled and included as part of the DSMC Standard Operating Procedures document.

6.5 Risks

6.5.1 Ranibizumab

Ranibizumab is well tolerated in people. More than 5000 study participants have been treated with injections of ranibizumab in clinical studies to date, however the full safety profile with long-term injections is not yet known. Some participants in ongoing clinical studies have developed inflammation in the eye (uveitis) which can be treated with anti-inflammatory drops. Increased eye pressure leading to glaucoma or cataract has also resulted from injections of ranibizumab. Other ocular adverse events that have occurred in ongoing clinical studies are believed to be due to the intravitreal injection itself and not the study drug. These are listed in section 6.5.2.

Some study participants have experienced systemic adverse events that may possibly be related to ranibizumab. Until cumulative safety data are analyzed, precise incidence figures are unknown and a causal relationship cannot be ruled out. These include arterial thromboembolic events and onset of hypertension. In a phase IIIb study to evaluate the long-term safety and efficacy of ranibizumab (The Safety Assessment of Intravitreous Lucentis for AMD, or SAILOR trial), which randomized patients with wet age-related macular degeneration to 0.5 mg ranibizumab or 0.3 mg ranibizumab, there was a higher rate of cerebrovascular stroke in the group that received the higher drug dose (1.2 vs 0.7%), although this trend did not achieve statistical significance.[43] It appeared that patients who had a prior history of stroke may be at greater risk for having a stroke after receiving ranibizumab, although there was a low incidence of stroke overall in this group. Additional data regarding systemic safety of ranibizumab in a diabetic population is also available from the DRCR.net Protocol I primary results.[36] This study enrolled a combined total of 375 patients in the two ranibizumab arms, who received an average of 8-9 intravitreal injections of 0.5 mg ranibizumab over the first year of treatment. There was no indication of an increased risk of cardiovascular or cerebrovascular events in the ranibizumab-treated study participants as compared with the triamcinolone-treated study participants or study participants who received no intravitreal drug. Indeed, lower rates of cardiovascular events as defined by the Antiplatelet Trialists' Collaboration were seen in the ranibizumab groups as compared with the sham group at both one (3% vs 8%) and two (5% vs 12%) years. Furthermore, a retrospective cohort study of 146,942 Medicare beneficiaries who received treatment for age-related macular degeneration did not find an increased risk of mortality, myocardial infarction, bleeding, or stroke from ranibizumab compared with laser therapy.[44]
There may be side effects and discomforts that are not yet known.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ranibizumab or its effect on fertility.

6.5.2 Potential Adverse Effects of Intravitreal Injection

Rarely, the drugs used to anesthetize the eye before the study drug injections (proparacaine, tetracaine, or xylocaine) can cause an allergic reaction, seizures, and an irregular heartbeat.

Subconjunctival hemorrhage or floaters will commonly occur as a result of the intravitreal injection. Discomfort, redness, or itching lasting for a few days is also likely.

Immediately following the injection, there may be elevation of intraocular pressure. It usually returns to normal spontaneously, but may need to be treated with topical drugs or a

paracentesis to lower the pressure. The likelihood of permanent loss of vision from elevated intraocular pressure is less than 1%.

As a result of the injection, endophthalmitis (infection in the eye) could develop. If this occurs, it is treated by intravitreal injection of antibiotics, but there is a risk of permanent loss of vision including blindness. The risk of endophthalmitis is less than 1%.

As a result of the injection, a retinal detachment could occur. If this occurs, surgery may be needed to repair the retina. The surgery is usually successful at reattaching the retina. However, a retinal detachment can produce permanent loss of vision and even blindness. The risk of retinal detachment is less than 1%.

The injection could cause a vitreous hemorrhage. Usually the blood will resolve spontaneously, but if not, surgery may be needed to remove the blood. Although the surgery usually successfully removes the blood, there is a small risk of permanent loss of vision and even blindness. The risk of having a vitreous hemorrhage due to the injection is less than 1%.

6.5.3 Risks of Focal/Grid Photocoagulation Treatment

Serious complications from laser treatment are rare. They occur in fewer than 1 in 1,000 cases. These include damage to the macula, bleeding inside the eye, immediate or delayed increase in pressure inside the eye, damage to the optic nerve, damage to the iris, damage to the lens or an intraocular lens, retinal hole, blindness, and loss of the eye. If a laser burn occurs too near the center of vision, a scotoma could develop. After several years, the scars caused by the laser may enlarge and may be associated with vision loss.

Anesthetic drops and a contact lens may be used as a part of the laser procedure. Risks include allergic reaction, infection, and corneal abrasion (scratch on the clear front surface of the eye). If any of these problems occur, they usually clear up rapidly.

6.5.4 Risks of Panretinal Photocoagulation Treatment

Panretinal photocoagulation can reduce peripheral and night vision. In addition, it can reduce transient or permanent central vision loss. Rarely, it can cause transient increase in intraocular pressure, presumably through secondary angle closure as the lens-iris diaphragm shifts forward with transient swelling of the posterior tissues.

In some cases retrobulbar or peribulbar injection may be used to anesthetize the eye and to reduce eye movements. Complications of retrobulbar and peribulbar injections are rare. They include, but are not limited to, the following: retrobulbar hemorrhage (bleeding behind the eyeball); perforation of the eye by the needle; damage to the optic nerve; diplopia lasting up to 24 hours or more; ptosis lasting up to 24 hours or more; difficulty speaking or breathing; lightheadedness/syncope/vasovagal response; allergy to any components of the injection; life threatening response due to the spread of anesthesia to the brain stem, resulting in seizures, drowsiness, confusion, loss of ability to talk, convulsions, stoppage of breathing, or stoppage of heartbeat. All of these complications are rare.

6.5.5 Risks of Eye Examination and Tests

There is a rare risk of an allergic response to the topical medications used to anesthetize the eye or dilate the pupil. Dilating drops rarely could cause an acute angle closure glaucoma attack, but

this is highly unlikely since the study participants in the study will have had their pupils dilated many times previously.

There are no known risks associated with OCT or fundus photographs. The bright flashes used to take the photographs may be annoying, but are not painful and cause no damage.

CHAPTER 7.
STATISTICAL METHODS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

7.1 Sample Size

The sample size estimate has been computed for the primary study objective, to determine whether visual acuity in the deferred PRP group is non-inferior to visual acuity in the prompt PRP group at 2 years. The primary analysis consists of a two-group comparison of mean change in visual acuity at 2 years, adjusted for baseline.

7.1.1 Sample Size Assumptions

For the cohort without center involved DME, the 2-year visual acuity outcomes for the prompt PRP group can be estimated using unpublished data from the ETDRS for eyes without center involved thickening on baseline photographs, with PDR on baseline photographs (level 61, 65), baseline visual acuity letter score ≥24 that were assigned to the full scatter group followed by focal/grid laser as needed (N=113). For the cohort with center involved DME, the 2-year visual acuity outcomes can be estimated using data from the ranibizumab groups in DRCR.net LRT for DME Study (Protocol I). Although the visual acuity and retinopathy severity status eligibility criteria differ between the current study and Protocol I, other key eligibility criteria between the two studies are the same. In addition, many eyes in Protocol I did have PDR although in that trial the investigator judged at baseline that the eye would not require PRP within 6 months. Therefore eyes in Protocol I with PDR at baseline may serve as the best available estimate for outcome rates in the current study for eyes with DME which will be treated with anti-VEGF.

Table 1 summarizes the 2 year data from both ETDRS cohort and the Protocol I cohort separately.

Table 1. 2 Year Visual Acuity Data		
	Protocol I	**ETDRS**
N with 2 year data, eyes with severe retinopathy at baseline	100	113
Standard Deviation of change	16	16
Correlation of baseline and change	-0.21	-0.24

The slightly more conservative estimates from DRCR.net were used for sample size estimation:

- Standard deviation: 16 letters (95% C.I.: 14, 19)
- Correlation: -0.21 (95% C.I.: 0, -0.38)

7.1.2 Non-Inferiority Margin

The non-inferiority margin specifies how much worse the anti-VEGF plus deferred PRP group could be than the prompt PRP group in the population with respect to the primary change in visual acuity outcome yet still be considered to be non-inferior. If the upper bound of the one-sided confidence interval around the difference (prompt PRP group minus anti-VEGF plus deferred PRP group) is less than this margin, indicating that a true difference between the groups

of a size equal to the margin (or larger) is unlikely, the anti-VEGF plus deferred PRP group will be considered non-inferior to the prompt PRP group.

Based on the objectives of this study and the potential deleterious effects on visual function by PRP, a non-inferiority margin of 5 letters was judged to be clinically acceptable. In addition, this margin is less than the lower limit of the 95% confidence interval for the comparison of immediate PRP with observation. This helps ensure that anti-VEGF with deferred PRP is superior to observation alone in the event that it is found to be non-inferior to prompt PRP.

7.1.3 Sample Size Estimations

Table 2: Sample Size Estimates Per Group using different parameters:
Alpha = 0.025, Power = 85%

Standard Deviation	Correlation	Non-Inferiority Margin	
		4	5
14	**0**	221	142
	-0.21	212	136
16	**0**	289	185
	-0.21	277	**177**
19	**0**	407	261
	-0.21	390	250

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

- Standard deviation of change in letter score = 16
- Correlation between baseline and change in visual acuity letter score = -0.21
- Type 1 error rate = 0.025 (1-sided)
- Power = 85%

With these assumptions, sample size has been calculated to be 177 eyes in each group. This sample size will be increased to 190 eyes per group (380 total eyes) to account for lost to follow-up. Assuming 20% of study participants have two study eyes (based on enrollment in previous DRCR.net studies), this equates with having approximately 316 study participants.

The primary analysis will adjust for correlation within study participants with two study eyes (projected to be 20% of the study participants); therefore, the actual power will be somewhat higher than 85%, depending on the degree of correlation and the number of study participants with two study eyes. In addition, since multiple imputation methods will be used for missing data at follow-up, as described below, the overall power may be increased above 85% since the sample size calculations include an adjustment for lost to follow-up.

7.2 Efficacy Analysis Plan

7.2.1 Principles for Analysis

The primary analysis will consist of a comparison of change in visual acuity in the prompt PRP group with the ranibizumab+deferred PRP group at the 2-year follow-up visit, using analysis of covariance to adjust for baseline visual acuity and generalized estimating equations (GEE) to account for the correlation within study participants with two study eyes. If the upper bound of

the one-sided 97.5% confidence interval on the difference in change in visual acuity between the two groups (prompt PRP group minus anti-VEGF plus deferred PRP group) lies below 5 letters, the null hypothesis that ranibizumab+deferred PRP is not non-inferior will be rejected at the 0.025 level.

The primary analysis will include all randomized eyes, according to the treatment group assignment at randomization. Missing data and treatment deviations will be handled as follows:

- For study participants who completed the 2-year visit and do not receive an alternate treatment for PDR, the 2-year data will be used.
    - Note: this includes any patients who meet the criteria above but do not receive all injections of the randomized treatment required by the protocol.
- For study participants who do not complete the 2-year visit and do not receive an alternate treatment, multiple imputation methods using all available data from Assessment Visits will be used to impute 2-year data.
- For all other study participants, i.e. those who receive an alternate treatment, multiple imputation methods, using only data from the last Assessment Visit prior to the administration of the alternate treatment, will be used to impute 2-year data. This includes eyes in the deferred group who get PRP before indicated by protocol. PRP treatment per protocol, intravitreal ranibizumab, or focal/grid laser are not considered alternate treatments.

Secondarily, a sensitivity analysis will be conducted as described above, except the 3rd group will be excluded. If the results of the two methods differ, exploratory analyses will be performed to evaluate the factors that have contributed to the differences.

The primary analysis will pool eyes with and without center involved DME at baseline. However, all analyses will be replicated in subgroups based on baseline central DME status.

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

Pre-planned subgroup analyses will be described in the detailed Statistical Analysis Plan and include stratification by presence of central-subfield involved DME, visual acuity, central subfield thickness, and prior DME treatment history. For eyes in which DME treatment was initiated, additional analyses will compare treatment group response rates based on adherence to the DRCR.net DME retreatment algorithm.

There are no data to suggest that the treatment effect will vary by gender or race/ethnicity. However, both of these factors will be evaluated in exploratory analyses.

Longitudinal analyses also will be conducted to assess trends over time.

The number of study participants per center is small for many centers, therefore center effects will not be included in the statistical model; however for centers with a large number of study

participants, the treatment effect will be assessed. If a positive overall effect of treatment is found, heterogeneity of treatment effect across centers will be explored using random center effects.

All linear model assumptions will be verified including linearity, normality of residuals, and homoscedasticity. If model assumptions are not met a nonparametric analysis will be considered.

7.2.2 Secondary Outcomes for Treatment Group Comparison

7.2.2.1 Visual Acuity

Visual acuity is the primary outcome variable. As described earlier, the primary outcome is the mean change in visual acuity at 2 years adjusted for the baseline acuity.

Additional analyses will be conducted on the visual acuity data to assess for consistency with the primary analysis. The additional analyses will include the following:

Table 2. Additional Analyses of Visual Acuity

Outcome	Analysis Technique
Success Proportion (Improvement ≥ 15 letters)	Logistic regression with GEE
Success Proportion (Improvement ≥ 10 letters)	Logistic regression with GEE
Failure Proportion (Worsening ≥ 15 letters)	Logistic regression with GEE
Failure Proportion (Worsening ≥ 10 letters)	Logistic regression with GEE
Visual Acuity Over Two Years	Area under the curve analysis

7.2.2.2 Visual Function Testing

Humphrey visual field testing (at select sites), NEI VFQ-25, and UAB-LLQ will be performed to assess visual function.

Analysis of Visual Function Questionnaire Data

A treatment group comparison of change in visual function subscale scores from baseline to 2 years (to coincide with the primary visual acuity outcome) will be performed using analysis of covariance with adjustment for baseline score. As visual function subscale scores are measured at the study participant level, data from bilateral participants is non-informative with respect to treatment effect; hence, bilateral participants will not be included in these analyses. The null hypothesis being tested will be the usual efficacy hypothesis of no difference in mean subscale score by treatment. To control for inflation in the type I error rate due to testing of multiple subscales, the following subscales that are hypothesized to be those most likely to differ by treatment group will be considered the primary subscales of interest: driving (NEI VFQ-25 and UAB-LLQ subscales), peripheral vision (NEI VFQ-25 single item and UAB-LLQ subscale), color vision (NEI VFQ-25 and UAB-LLQ single items), and general dim lighting (UAB-LLQ subscale). Evidence of a treatment difference on these scales will be interpreted as definitive evidence of a treatment group difference with respect to the subscale in question. To further

control for multiple testing, only p-values less than 0.01 will be considered statistically significant evidence for a treatment difference.

All other subscales from the NEI-VFQ and UAB-LLQ will be analyzed similarly to the primary subscales; however, statistically significant differences on these subscales will be considered suggestive of treatment group differences rather than definitive. In addition to the analysis of 2 year data, a longitudinal analysis of subscale scores that includes all annual visits will also be performed using linear mixed models to account for correlation within participant over time. The purpose of this analysis will be to determine whether there are significant trends over the 5 years, and whether any treatment group differences identified at 2 years are consistently maintained throughout the 5 year follow up period.

Analysis of Visual Field Testing Data

A treatment group comparison of total point score will be performed using the same analysis methods proposed for the visual function subscale scores. Bilateral participants will be included in these analyses. The central (30 degree) and peripheral (30-60 degree) fields will be analyzed combining both fields, and also analyzed separately.

7.2.2.3 Diabetic Retinopathy Outcomes

The treatment groups will be compared on the following key diabetic retinopathy outcomes of interest at the 2 year visit:

- Need for supplemental PRP after completion of initial deferred or prompt PRP
- Need for vitrectomy
- Development of neovascular glaucoma
- Percent of eyes with vitreous hemorrhage
- Proportion of eyes with complete regression of neovascularization on fundus photography

Binary outcomes will be analyzed using logistic regression models and GEE to account for the potential correlation between two study eyes.

Within the ranibizumab+deferred PRP group the following outcome will be assessed. 95% confidence intervals will be constructed.

- Proportion of eyes not requiring PRP by 2 years.

7.2.2.4 Macular Thickness

Retinal thickening outcomes will be assessed from the OCT central subfield and retinal volume. For each eye, the change in central subfield OCT retinal thickness and change in retinal volume from baseline will be computed. A treatment group comparison on the following outcomes will be performed:

- Change in OCT central subfield thickness
- Change in OCT retinal volume
- Proportion of eyes with OCT central subfield thickness of ≥250 µm on Stratus OCT (or standard deviation equivalent) and at least a 25µm increase from baseline

Binary outcomes will be analyzed using logistic regression models adjusting for baseline factors where appropriate and GEE to account for the correlation between two study eyes. Continuous

outcomes will be analyzed using an analysis of covariance model adjusting for baseline measures where appropriate and GEE to account for the potential correlation between two study eyes.

7.2.2.5 Economic Analysis

The purpose of the economic analysis is to compare the treatment groups with respect to cost, cost consequences, and cost utility. The viewpoint adopted is that of a third party payer. For the cost-consequence and cost-utility analyses we have adopted a perspective that includes patient and broader societal issues, particularly focusing on workplace productivity loss.

Cost Consequence Analysis

Data from the clinical trial on number of clinic visits completed, number of procedures performed (e.g. OCT, fundus photographs), number of PRP treatments, and number of ranibizumab treatments will be used to estimate an average cost per patient for each treatment arm, using the Medicare Fee Schedule to estimate medical costs. The cost estimates in combination with the data on functional outcomes and percent productivity loss (without applying a monetary value) for each treatment arm will be incorporated into a cost consequence analysis. While, in theory, the set of functional outcomes can all be subsumed by a health-related quality of life measure, we treat it as a cost-consequence analysis because there are specific elements of vision-related function that are important to track and to value individually against the costs of the intervention. For this analysis, the estimated average treatment group difference in costs is stated, with variation being characterized by variation in the quantity of services, which will be reported as a 95% confidence interval. In addition, we will state the observed treatment group differences in the functional outcomes and percent productivity loss and their 95% confidence intervals. This provides a summary of the functional benefits, if any, that are obtained with the more costly treatment. The functional outcomes of interest are differences by treatment group with respect to:

- Proportion of participants driving at baseline who stopped driving wholly or partly due to vision
- Proportion of participants driving at night at baseline who stopped driving at night wholly or partly due to vision
- Mean change from baseline in NEI VFQ-25 driving subscale score
- Mean change in UAB-LLQ driving subscale score
- Mean change in UAB-LLQ general dim lighting subscale score
- Mean change in NEI VFQ-25 peripheral vision subscale score
- Mean change in UAB-LLQ peripheral vision subscale score
- Mean change in NEI VFQ-25 color vision subscale score
- Mean change in UAB-LLQ color vision subscale score
- Mean change in percent work time missed due to vision problems over the past week
- Mean change in percent impairment while working due to vision problems over the past week
- Mean change in percent overall work impairment due to vision problems over the past week
- Proportion of participants losing 10 or more letters of visual acuity
- Difference in percent of productivity loss of subjects as measured by the WPAI

For functional outcomes measured at the participant level, data from bilateral participants is non-informative with respect to the treatment comparison and will not be included in the analyses. For outcomes measured at the eye level, data from bilateral participants will be included. Estimates of treatment effect will be adjusted for baseline level of the outcome. The cost consequence analysis will be conducted based on 1 year and 2 year data for all outcomes. In addition, the cost consequences with respect to the work outcomes will be calculated for each work outcome assessment visit and at 4 weeks from randomization.

Cost Utility Analysis

Data from the time trade-off questionnaire will be used to calculate patient-level preferences for vision at baseline and each annual follow-up visit and to derive a quality-adjusted life year (QALY) measurement for each patient at these time points. The change from baseline will be calculated for each patient and averaged by treatment group adjusting for baseline using analysis of covariance. Only unilateral participants will be included in the analysis. The difference in average medical care costs for each treatment group divided by the difference by treatment group in the average change in QALY score from baseline will form the estimated incremental cost utility ratio (ICUR). The uncertainty in the estimate of the incremental cost-utility ratio will be represented by bootstrapping the analysis and repeating the incremental cost-utility calculation with each bootstrapped dataset. The bootstrapped incremental costs and incremental effects can be graphed in a plane or represented as a cost-effectiveness acceptability curve.

While there is debate over whether to include measures of productivity as part of the cost in a cost-effectiveness or cost-utility analysis, we have the option of including the monetized value of productivity loss as captured by the Workplace Productivity and Activity Impairment instrument. Including costs in the numerator of the cost-effectiveness ratio may be relevant if a more intense treatment requires a significant time commitment, which is useful to capture. Alternatively, if there is a substantial change in individuals' productivity as a result of treatment, an analysis can be done to determine whether the increase in productivity is sufficient to offset the cost of the more expensive treatment. We can use a non-parametric test to compare costs with costs saved.

7.2.3 Safety Analysis Plan

Adverse events will be categorized as study eye, non-study eye, and systemic. The events will be tabulated separately for the two treatment groups. Adverse events of interest will include:

- Injection-related: endophthalmitis, tractional retinal detachment, rhegmatogenous retinal detachments, retinal tears, cataract, intraocular hemorrhage
- Ocular drug-related: inflammation, cataract, cataract surgery, increased intraocular pressure, new or worsening neovascular glaucoma, glaucoma medications, glaucoma surgery, new or worsening tractional retinal detachment, progression of tractional retinal detachment from extramacular to macular, new or worsening neovascularization of the iris
- Systemic drug-related: hypertension, cerebrovascular events, and cardiovascular events as defined by the Antiplatelet Trialists' Collaboration
    - *Systemic adverse events for participants with two study eyes will be evaluated separately from participants with one study eye.*

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

7.2.4 Additional Tabulations and Analyses

The following will be tabulated according to treatment group:

- Baseline demographic and clinical characteristics
- Visit completion rate for each visit
- Protocol deviations

Additional analyses mimicking the primary and secondary outcomes at 104 weeks will be conducted at 156 weeks, 4 years, and 5 years.

7.2.5 Interim Analysis Plan

A formal plan for interim analyses will be established in consultation with the DSMC.

CHAPTER 8. REFERENCES

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