Diabetic Retinopathy Clinical Research Network

Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy

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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

Diabetic Retinopathy (DR) is the leading cause of visual loss and new-onset blindness in the United States for those 20 through 74 years of age.[1] As of 2010, 3.63 million people worldwide are estimated to have at least moderate vision loss due to the complications of DR, and 850 thousand are estimated to suffer from blindness due to DR.[2] Proliferaitve diabetic retinopathy (PDR) can lead to vitreous hemorrhage (VH) which may affect vision and is a leading indication for vitrectomy. Vitreous hemorrhage also can preclude performing panretinal photocoagulation (PRP), as well as the evaluation and treatment of other diabetic and non-diabetic retinal pathology such as diabetic macular edema (DME) and age-related macular degeneration. Even in the modern era of using either PRP or anti-vascular endothelial growth factor (anti-VEGF) therapy to treat PDR, a Diabetic Retinopathy Clinical Research Network (DRCR.net) clinical trial showed that 27% to 34% of eyes developed VH over 2 years even after treatment was initiated with either anti-VEGF or PRP, respectively.[3] Given the increasing prevalence of diabetes in the United States and worldwide, the public health impact of PDR and its complications are large.[2, 4]

1.1.2 Treatment Options for VH from PDR

Although VH by itself is not detrimental to the eye, rapid clearance of the hemorrhage is desirable for both functional and anatomic reasons and also allows evaluation and treatment of the eye for other pathology such as DME. Functional central and peripheral visual acuity (VA) is commonly affected adversely by intraocular hemorrhage. As long as the retinal status remains stable, VA usually improves once the blood resolves. However, vitreous traction on or contraction of fibrous proliferans associated with retinal neovascularization, leading to VH, can lead to further complications causing VA loss if left unchecked. Prior to the advent of anti-VEGF therapy, in most cases of VH, PRP was performed as soon as the media cleared sufficiently to allow visibility and laser uptake. The goal of the PRP was to achieve regression of new vessels or at least stabilization of the neovascularization in order to decrease the probability of new or worsening VH or traction or rhegmatogenous retinal detachment while further clearing of the hemorrhage occurred. PRP generally leads to regression or quiescence of retinal neovascularization after a limited number of treatments and results in a reduction of severe vision loss over 5 years to rates as low as 4%. [5]

Although PRP has been the standard care for PDR for several decades, results from the DRCR.net Protocol S (Prompt Panretinal Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy) published in November 2015 suggest that anti-VEGF therapy is a safe and effective treatment alternative for PDR, with advantages over PRP in reductions in visual field sensitivity loss, need for vitrectomy and development of DME.[3] This study demonstrated non-inferiority of mean visual acuity letter improvement at 2 years for eyes treated with ranibizumab and deferred PRP as compared to those given prompt PRP for baseline PDR (difference +2.2, 95% confidence interval [CI]: -0.5 to +5.0, non-inferiority $P<0.001$). Although visual change at 2 years was not superior in the anti-VEGF group, the average visual acuity over 2 years (area under the curve) was significantly better in eyes that received anti-VEGF with a mean treatment group difference of +4.2 (95% CI:

+3.0 to +5.4, P<0.001). In addition, eyes that underwent prompt PRP had greater visual field sensitivity loss (mean dB difference 372; 95% CI: 213 to 531, P<0.001), more frequent vitrectomy (15% versus 4%, difference 9%, 95% CI: 4% to 15%, P<0.001), and, among those without DME causing VA loss at baseline, were more likely to develop DME causing VA loss (28% versus 9%, difference 19%, 95% CI: 10% to 28%, P<0.001) over the course of 2 years.

Two approaches for the management of VH from PDR are vitrectomy and treatment with anti-VEGF agents, the latter being highly effective even at small doses in regressing PDR.[6] Although clinical results suggest that both these methods are effective at improving retinal neovascularization, to date there has not been a randomized clinical trial with head to head comparison of their relative efficacy in improving VA in eyes with VH from PDR.

A standard approach for treatment of VH associated with PDR is to proceed to prompt vitrectomy in order to provide the fastest possible improvement in VA. Vitrectomy, or surgical removal of the vitreous gel and associated hemorrhage, enables rapid clearance of VH and concurrent delivery of panretinal endolaser. In cases in which traction retinal detachments or rhegmatogenous detachments occur, vitrectomy can also eliminate extensive neovascularization and treat existing retinal detachments.[7] Many advances in instrumentation and technique have resulted in dramatically faster surgical times, easier patient recovery and a reduction in complications over the last few decades.[8] In particular, the advent of 23 gauge surgical techniques, and smaller, have resulted in smaller surgical incisions and the possibility of sutureless surgery in addition to smaller instruments that allow more delicate manipulations of fibrovascular retinal tissue.[8] According to Castellarin et al, surgical complications still remain, including recurrent hemorrhage,[9] neovascular glaucoma, retinal detachment, fibrinoid syndrome, endophthalmitis and hypotony with subsequent phthisis bulbi.[10] It should be noted that many reports of vitrectomy outcomes in the diabetic population combine results from eyes with complex traction retinal detachments together with those from uncomplicated VH.[11, 12] However, data acquired from a cross-sectional population based study in the United Kingdom suggest that eyes with simple VH have substantially better functional and anatomic outcomes than those with any component of traction retinal detachment.[13]

The Diabetic Retinopathy Vitrectomy Study from the 1980s found a benefit for early vitrectomy within 6 months as compared to delayed vitrectomy after 12 months, particularly in eyes of type 1 diabetic patients with severe vision loss from dense VH.[14] In addition, a retrospective comparison of immediate versus delayed vitrectomy for VH from PDR found that although final vision did not differ significantly between the groups, the area under the curve for logMAR visual acuity from first presentation to last follow-up was significantly greater, meaning more time with decreased vision, for eyes that had delayed versus immediate vitrectomy, suggesting a possible visual benefit over time in eyes undergoing vitrectomy sooner.[15] Recent large scale, multi-center randomized trials of vitrectomy for the sole indication of VH from PDR are lacking. At this time, there is rationale for comparing current outcomes utilizing newer surgical techniques to alternative treatment modalities for PDR associated VH, including anti-VEGF therapy.

VEGF is a major causative factor in eye diseases that are characterized by neovascularization or increased vascular permeability, such as DR.[16-25] Anti-VEGF drugs are highly effective at causing regression of retinal neovascularization, and therefore can be useful in cases of VH due to PDR by reducing the chance of additional VH or traction or rhegmatogenous retinal detachments from new vessels. Once the hemorrhage is reabsorbed and the neovascularization is

temporarily stabilized by the anti-VEGF drug, either PRP can be completed or a longer-term course of anti-VEGF can be initiated to increase the chance of permanent regression of the PDR and lower the likelihood of subsequent VH or traction detachment of the macula or both without having to perform vitrectomy.

Anti-VEGF therapy has been evaluated in eyes with VH from PDR in the DRCR.net Protocol N (An Evaluation of Intravitreous Ranibizumab for Vitreous Hemorrhage Due to Proliferative Diabetic Retinopathy), although the endpoint of this study was short-term avoidance of vitrectomy (16 weeks after randomization) rather than VA recovery.[26] This study compared the safety and efficacy of anti-VEGF treatment with saline injection for prevention of vitrectomy in eyes with VH from PDR. Although Protocol N did not show a difference in vitrectomy rates at 16 weeks comparing ranibizumab with saline injections, both treatment groups had lower than expected vitrectomy rates (12% vs. 17% respectively), and the ranibizumab group had greater visual acuity improvements (22±23 vs. 16±31, P = 0.04), increased PRP completion rates (44% vs. 31%, P = 0.05), and a reduced rate of recurrent VH (6% vs. 17%, P = 0.01) compared with saline injections. [26] Therefore, it is possible that anti-VEGF drugs have at least a short term biologic effect. Rates of vitrectomy at 16 weeks in Protocol N were substantially lower than those suggested by previous studies with observation arms, suggesting that the management of eyes with VH from PDR with anti-VEGF therapy might avoid further surgical intervention in many eyes. Indeed, by 52 weeks (with 12 weeks through 52 weeks of treatment at investigator discretion), only 40% of eyes in both groups received vitrectomy; thus, by 1 year approximately 60% of eyes did not need vitrectomy. The efficacy of anti-VEGF treatment in allowing clearance of VH while avoiding surgery, especially in eyes that have already received PRP is supported by another recent case series, which reported treatment with bevacizumab in 18 eyes of 18 patients with new onset VH after previous full PRP.[27] By 12 months, 72.2% of eyes had complete clearing of VH. However, although 9 (50%) of the eyes gained vision, overall there was no statistically significant visual gain over 12 months (mean best corrected VA improved from 1.32±1.03 to 1.09±1.10 logMAR, p = 0.433), and 2 eyes (11%) had severe vision loss of 3 or more lines of vision due to traction retinal detachment.

1.1.3 Aflibercept

The anti-VEGF agent to be used in this trial is intravitreous aflibercept injection, also known as VEGF Trap-Eye or Aflibercept (Eylea®), which is a soluble decoy receptor fusion protein that has a high binding affinity to all isoforms of VEGF as well as to placental growth factor. Aflibercept received approval by the United States Food and Drug Administration (FDA) for the treatment of neovascular age-related macular degeneration in 2011[28], treatment of macular edema due to central retinal vein occlusion in 2012[29-31], and treatment of macular edema due to branch retinal vein occlusion and treatment of DME in 2014.[32]

Based on data from the VIVID and VISTA phase III DME studies, aflibercept also became approved for treatment of diabetic retinopathy in patients with DME in 2015. Change in diabetic retinopathy severity level among eyes with DME and DR at baseline was a pre-specified secondary efficacy outcome, and the proportion of patients improving by at least 2 steps was significantly greater in aflibercept-treatment groups compared to the control group at 100 weeks in both trials.[33]

Although there is no currently available head-to-head data on the available anti-VEGF agents for treatment of PDR, a comparative effectiveness trial in DME reported that aflibercept was more

effective than ranibizumab and bevacizumab in improving vision in eyes starting with CI-DME and worse levels of visual acuity (approximately 20/50 or worse).[34]

1.1.4 Summary of Study Rationale

Although VH from PDR can cause acute and dramatic vision loss for patients with diabetes, there is no current, evidence-based clinical guidance as to what treatment method is most likely to provide the best visual outcomes once intervention is desired. Intravitreous anti-VEGF therapy alone or vitrectomy combined with intraoperative PRP each provide the opportunity to stabilize or regress retinal neovascularization. However, clinical trials are lacking to elucidate the relative time frame of visual recovery or final visual outcome in prompt vitrectomy compared with initial anti-VEGF treatment. The DRCR.net Protocol N demonstrated short-term trends consistent with a possible beneficial effect of anti-VEGF treatment in eyes with VH from PDR, including greater VA improvement and reduced rates of recurrent VH as compared with saline injection. It is possible that a study with a longer duration of follow-up with structured anti-VEGF retreatment would demonstrate even greater effectiveness of anti-VEGF for VH to avoid vitrectomy and its attendant adverse events while also improving visual acuity. On the other hand, advances in surgical techniques leading to faster operative times, quicker patient recovery, and reduced complication rates may make prompt vitrectomy a more attractive alternative since it results in the immediate ability to clear hemorrhage and to perform PRP if desired, often as part of one procedure. This proposed study will evaluate the safety and efficacy of two treatment approaches for eyes with VH from PDR: prompt vitrectomy + PRP and intravitreous aflibercept injections.

1.2 Study Objectives

The objectives of this study are to 1) evaluate and compare visual acuity outcomes over the course of the study of a prompt vitrectomy + PRP regimen and an intravitreous aflibercept regimen in eyes with VH from PDR for which intervention is deemed necessary, and 2) characterize the follow-up course for the two treatment regimens, including but not limited to post-operative complications for the vitrectomy group, and number of injections needed and percent requiring vitrectomy in the intravitreous aflibercept group.

1.3 Study Design and Synopsis of Protocol

A. Study Design

- Multi-center randomized clinical trial

B. Major Eligibility Criteria

- Age >=18 years
- Type 1 or type 2 diabetes
- Study eye with:
    - Vitreous hemorrhage causing vision impairment, presumed to be from proliferative diabetic retinopathy, for which intervention is deemed necessary
        - *Note: Prior PRP is neither a requirement nor an exclusion*
    - Best corrected visual acuity letter score 78 or worse (approximate Snellen equivalent 20/32 or worse) with at least light perception
        - *Investigators should use particular caution when considering enrollment of an eye with visual acuity letter score 78 to 69 (approximate Snellen*

equivalent 20/32 to 20/40) to ensure that the need for vitrectomy and its potential benefits outweigh the potential risks.

- No evidence of rhegmatogenous retinal detachment or evidence of traction retinal detachment involving or threatening the macula
  - *If the density of the hemorrhage precludes a visual assessment on clinical exam to confirm eligibility, then it is recommended that assessment be performed with ultrasound as standard care.*
- No history of vitrectomy

C. Treatment Groups

Eligible eyes, one per participant, will be assigned randomly (1:1) to one of the following groups:

A. Intravitreous 2 mg aflibercept injections
B. Prompt vitrectomy + PRP

For the intravitreous aflibercept group, the initial injection must be given on the day of randomization. Follow-up injections will be performed as often as every 4 weeks unless criteria for deferral are met (see section 4.3.1). Vitrectomy and PRP can only be performed if protocol criteria are met (see sections 4.3.2 and 4.3.3).

For the prompt vitrectomy + PRP group, the vitrectomy must be scheduled to be performed within 2 weeks of randomization. Vitrectomy will be performed according to the investigator's usual routine, including pre-operative care, surgical procedure, and post-operative care, although anti-VEGF may not be given post-operatively unless there is recurrent hemorrhage (see section 4.5.2).

D. Sample Size

A minimum of 200 study eyes, one per participant, will be randomized.

E. Duration of Follow-Up

Primary outcome: 24 weeks
Total duration: 104 weeks

F. Follow-up Schedule

- **Outcome Visits:**

  All participants in both groups will have visits at the following times post-randomization:
  - Year 1: 4, 12, 24, 36, 52 weeks
  - Year 2: 68 weeks, 84 weeks, 104 weeks

  It is recognized that the time between initial treatment and outcome visits will differ between the two groups due to the timing of the initial treatment; however, the differential timing of treatments is representative of clinical care in which anti-VEGF can be given immediately and vitrectomy would need to be scheduled in advance. Therefore, the area under the curve analysis will be representative of clinical care based on the time point that the decision is made to intervene.

- **Treatment Visits:**

- Participants receiving intravitreous aflibercept also will have treatment assessment visits as often as every 4 weeks, depending on recent treatment administered.

➢ **Additional Visits:**

- Participants undergoing vitrectomy will have a study visit 1 week post-vitrectomy for safety evaluation. Investigators may schedule an initial (e.g. 1 day) post-operative visit earlier as standard care at their discretion.

G. Main Efficacy Outcomes

Treatment Group Comparisons

Primary Outcome: Visual acuity area under the curve between randomization and 24 weeks

Additional Key Outcomes (at 24, 52, and 104 weeks unless otherwise indicated):

- Visual acuity area under the curve between randomization and 52 and 104 weeks
- Mean visual acuity at 4, 12, and 24 weeks, and annual visits
- Percent 20/20 or better, 20/32 or better, 20/40 or better, 20/200 or worse, and 20/800 or worse at 4, 12, and 24 weeks, and annual visits
- Proportion of eyes with at least 15 and at least 30 letter gains or losses from baseline
- Rates of recurrent VH on clinical exam
- Percentage of eyes with retinal neovascularization
- Mean OCT central subfield thickness
- Treatment and follow-up costs
- Mean change in four Workplace Productivity and Activity Impairment Questionnaire (WPAIQ) scales and area under the curve analyses of the Work Productivity Loss and Activity Impairment scales at 4, 12, and 24 weeks, and annual visits

Key Outcomes within Treatment Groups

- Percent undergoing vitrectomy (initial vitrectomy in aflibercept group or repeat vitrectomy in vitrectomy group)
- Number of aflibercept injections performed
- Percent receiving PRP (aflibercept group only)

The primary outcome of visual acuity area under the curve at 24 weeks was primarily selected for sample size considerations. The long-term additional key outcomes and within-group outcomes will be equally important as the area under the curve outcome for evaluating the overall follow-up course for these two treatment approaches. Therefore, publication is not planned until the full 104 week follow-up has closed.

H. Main Safety Outcomes

Ocular: endophthalmitis, retinal detachment, visually significant cataract, cataract surgery

Systemic: Antiplatelet Trialist Collaboration (APTC) events

I. Schedule of Study Visits and Procedures

Visit window	0	1w post-vitrectomy* ±3d	Treatment Assessment Visits** ±1w	Non-Annual Outcome Visits† ±1 to4w	24-Week Visit and Annual visits ±4w
E-ETDRS best corrected visual acuity[a]	X		X	X	X
OCT[b]	X		X	X	X
Ultrasound[c]	X	X	X	X	X
Eye exam[d]	X	X	X	X	X
Blood pressure	X				X
HbA1c[e]	X				X
Questionnaire[f]	X			X	X
Vitreous/aqueous sampling[g]	X*				

*Vitrectomy group at baseline and aflibercept group if vitrectomy is performed during follow-up

**Every 4 to 16 weeks, as needed, for eyes receiving aflibercept

†At 12, 36, 68 and 84 weeks

a=both eyes including protocol refraction in the study eye only at outcome visits and DME treatment visits and on both eyes at 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=study eye only; at annual visits and if evaluating for DME treatment

c= study eye only if needed as part of standard care if the density of the vitreous hemorrhage precludes assessment of retinal detachment.

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

e=can be obtained up to 3 weeks after randomization; does not need to be repeated if HbA1c is available from within the prior 3 months

f= Workplace Productivity and Activity Impairment Questionnaire

g=if investigator has agreed to perform sample collection and participant consents to this ancillary component; participants will be given the option of providing vitreous sample only or both vitreous and aqueous samples at the time of vitrectomy.

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, OCT Procedures Manual, and Study Procedures Manual) provide details of the examination procedures and intravitreous injection procedure.

Visual acuity testers will be masked to treatment group at all outcome visits. Investigators and study participants are not masked to treatment group.

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.

A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

The risk level is considered to be research involving greater than minimal risk.

CHAPTER 2. STUDY PARTICIPANT ELIGIBILITY AND ENROLLMENT

2.1 Identifying Eligible Participants and Obtaining Informed Consent

A minimum of 200 eyes (1 per participant) are expected to be enrolled into the randomized trial. 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 either of the two treatment groups, including ability to undergo vitrectomy within 2 weeks of randomization.

2.2 Participant Eligibility Criteria

2.2.1 Participant-level Criteria

Inclusion

To be eligible, the following inclusion criteria must be met:

1. Age >= 18 years
   - *Participants <18 years old are not being included because proliferative diabetic retinopathy is so rare in this age group that the diagnosis 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.
5. Patient is willing and able to undergo vitrectomy within next 2 weeks and the vitrectomy can be scheduled within that time frame.

Exclusion

A potential participant is not eligible if any of the following exclusion criteria are present:

6. History of chronic renal failure requiring dialysis (including placement of fistula if performed in preparation for dialysis) or kidney transplant.
7. 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).
8. Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior to randomization or plans to do so in the next 4 months.
9. A condition that, in the opinion of the investigator, would preclude participant undergoing elective vitrectomy surgery if indicated during the study.
10. 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: participants cannot receive another investigational drug while participating in the study.*
11. Known allergy to any component of the study drug or any drug used in the injection prep (including povidone iodine).
12. Blood pressure > 180/110 (systolic above 180 or diastolic above 110).
    - *If blood pressure is brought below 180/110 by anti-hypertensive treatment, potential participant can become eligible.*
13. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.
    - *These drugs cannot be used during the study.*
14. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next two years.
    - *Women who are potential participants should be questioned about the potential for pregnancy. Investigator judgment is used to determine when a pregnancy test is needed.*
15. Potential participant is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the two years.

2.2.2 Study Eye Criteria

The participant must have at least one eye meeting all of the inclusion criteria and none of the exclusion criteria listed below.

A participant can have only one study eye. If both eyes are eligible at the time of randomization, the study eye will be selected by the investigator and participant before randomization.

The eligibility criteria for a study eye are as follows:

Inclusion

a. Vitreous hemorrhage causing vision impairment, presumed to be from proliferative diabetic retinopathy, for which intervention is deemed necessary.
   - *Note: Prior PRP is neither a requirement nor an exclusion.*
   - *Subhyaloid hemorrhage alone does not make an eye eligible; however, presence of subhyaloid hemorrhage in addition to the criteria above will not preclude participation provided the investigator is comfortable with either treatment regimen.*

b. Immediate vitrectomy not required (investigator and participant are willing to wait at least 4 months to see if hemorrhage clears sufficiently with anti-VEGF without having to proceed to vitrectomy).

c. Visual acuity letter score ≤78 (approximate Snellen equivalent 20/32) and at least light perception.
   - *Investigators should use particular caution when considering enrollment of an eye with visual acuity letter score 69 to 78 (approximate Snellen equivalent 20/32 to 20/40) to ensure that the need for vitrectomy and its potential benefits outweigh the potential risks.*

Exclusion

d. Evidence of traction detachment involving or threatening the macula.
   - *If the density of the hemorrhage precludes a visual assessment on clinical exam to confirm eligibility, then it is recommended that assessment be performed with ultrasound as standard care.*

e. Evidence of rhegmatogenous retinal detachment.
   - *If the density of the hemorrhage precludes a visual assessment on clinical exam to confirm eligibility, then it is recommended that assessment be performed with ultrasound as standard care.*

f. Evidence of neovascular glaucoma (iris or angle neovascularization is not an exclusion).

g. Known diabetic macular edema (DME), defined as either
   i. OCT central subfield thickness (microns):
      1. Zeiss Cirrus: ≥290 in women; ≥305 in men
      2. Heidelberg Spectralis: ≥305 in women; ≥320 in men

      OR

   ii. DME on clinical exam that the investigator believes currently requires treatment.

h. History of intravitreous anti-VEGF treatment within 2 months prior to current vitreous hemorrhage onset or after onset.

i. History of intraocular corticosteroid treatment within 4 months prior to current vitreous hemorrhage onset or after onset.

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

k. History of vitrectomy.

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

m. Aphakia.

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

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

2.2.3 Non-Study Eye Criteria

If anti-VEGF treatment is indicated for any condition in the non-study eye at any time during the study, the investigator must be willing to use the study anti-VEGF drug (2 mg aflibercept) for the non-study eye. If the non-study eye is currently being treated with a different anti-VEGF drug for any condition, then the investigator and patient must be willing to switch to aflibercept. If the investigator or patient is unwilling to change anti-VEGF treatment in the non-study eye, the patient should not be enrolled.

2.3 Screening Evaluation and Baseline Testing

2.3.1 Historical Information

A history will be elicited from the 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 and Study Procedures Manual). Visual acuity testing and ocular exam will be performed by DRCR.net certified personnel.

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye. *(on day of randomization)*
    - *If the E-ETDRS visual acuity letter score is 0, then counting fingers, hand motion, and light perception are assessed.*
2. Workplace Productivity and Activity Impairment Questionnaire (*on day of randomization*).
3. OCT on the study eye *(within 8 days prior to randomization)*
    - *Unless insufficient view precludes obtaining an accurate measurement*
4. Ocular examination of each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(on day of randomization)*
5. B-Scan ultrasound as part of standard care on the study eye if the density of the vitreous hemorrhage precludes assessment of traction or rhegmatogenous retinal detachment
6. Measurement of blood pressure
7. Laboratory testing- HbA1c

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

2.4 Enrollment/Randomization of Eligible Participants

1. Prior to randomization, the 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 injection must be given on the day of randomization and vitrectomy must be performed within 2 weeks, depending on treatment group; therefore, a participant should not be randomized until this is possible.
3. Randomization is completed on the DRCR.net website.

- Study eyes will be randomly assigned (stratified by site) with equal probability to one of two treatment groups:
    - Group A: Intravitreous 2 mg aflibercept injections
    - Group B: Prompt vitrectomy + PRP

CHAPTER 3. FOLLOW-UP VISITS AND TESTING

3.1 Visit Schedule

The schedule of protocol-specified follow-up visits is as follows:

- **Outcome Visits:**
  All participants in both groups will have visit at the following time points post-randomization:
  - Year 1: 4 (±1) weeks, 12 (±4) weeks, 24(±4) weeks, 36 (±4) weeks, 52(±4) weeks
  - Year 2: 68 (±4) weeks, 84 (±4) weeks, 104 (±4) weeks

- **Vitreous Hemorrhage Treatment Assessment Visits:**

  Aflibercept Group
  Participants in the aflibercept group, will have treatment assessment visits as often as every 4 weeks, depending on treatment administered:
  - Visits every 4±1 weeks for the first 24 weeks and as long as injections are given (with a minimum of 21 days between injections).
  - After 24 weeks, if the injection is deferred at the current and previous 2 visits (see section 4.3.1 for retreatment criteria), 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, the next study follow-up visit is in 4 weeks.

  Vitrectomy Group
  Eyes for which aflibercept is initiated for recurrent hemorrhage post-vitrectomy will have treatment assessment visits as often as every 4 weeks until the hemorrhage has cleared or repeat vitrectomy is performed (see section 4.5.2).

- **DME Treatment Visits**
  - If aflibercept for DME has been initiated, follow-up visits for DME treatment occur every 4 weeks for the first 24 weeks from initial aflibercept treatment for DME. After 24 weeks, if the injection is deferred at the current and previous 2 visits (see section 4.7 for retreatment criteria), 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, the next study follow-up visit is in 4 weeks.

- **Additional Protocol Visits:**
  Participants undergoing vitrectomy will have a study visit 1 week (±3 days) post-vitrectomy for safety evaluation only. Investigators may schedule an initial (e.g. 1 day) post-operative visit earlier as standard care.

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

3.2 Testing Procedures

The 1-week post-operative visit will include a safety evaluation only. Otherwise, the following procedures will be performed at each protocol-specified visit on the study eye only, unless otherwise specified. A grid in section 1.3 summarizes the testing performed at each visit.

1. E-ETDRS visual acuity testing (best corrected) in each eye.
   - A protocol refraction in the study eye is required at Outcome Visits (listed above) and DME treatment 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. Workplace Productivity and Activity Impairment Questionnaire (WPAIQ) at all outcome visits (listed above).
3. OCT at the 24-week visit, annual visits, and DME treatment visits only.
   - *Unless insufficient view precludes obtaining an accurate measurement.*
4. Ocular exam, including slit lamp examination (including 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 ≥ 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).*
5. B-Scan ultrasound as needed as part of standard care if vitreous hemorrhage precludes ability to assess for traction or rhegmatogenous retinal detachment.
6. Laboratory testing of Hemoglobin A1c at the 24-week visit and annual visits only.
   - *HbA1c does not need to be repeated if available in the prior 3 months.*
7. Blood pressure at the 24-week visit and annual visits only.

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 unscheduled 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:

- Intravitreous 2 mg aflibercept injections
- Prompt vitrectomy + PRP

For the intravitreous aflibercept group, the initial injection must be given on the day of randomization. Follow-up injections will be performed as often as every 4 weeks according to the retreatment criteria below. Vitrectomy and PRP can only be performed if protocol criteria are met.

For the prompt vitrectomy + PRP group, the vitrectomy must be scheduled within 2 weeks of randomization. The vitrectomy procedure and follow-up treatment are described below.

4.2 Intravitreous Injections

4.2.1 Inravitreous Aflibercept Injection (Eylea®)

Eylea® (intravitreal aflibercept injection) is made by Regeneron Pharmaceuticals, Inc. and is approved by the FDA for the treatment of neovascular age-related macular degeneration, macular edema due to central retinal vein occlusion, macular edema due to branch retinal vein occlusion, diabetic macular edema, and diabetic retinopathy in eyes with diabetic macular edema.

Study eyes that receive anti-VEGF will receive a dose of 2 mg aflibercept in 0.05 cc each time a study injection is performed. The physical, chemical and pharmaceutical properties and formulation are provided in the Clinical Investigator Brochure. Aflibercept for the study and non-study eye will be distributed by the Network.

4.2.2 Intravitreous Injection Technique

The injection is preceded by a povidone iodine prep of the conjunctiva. In general, topical antibiotics in the pre-, peri-, or post-injection period should not be used.

The injection will be performed using sterile technique. The full injection procedure is described in the DRCR.net Study Procedures Manual.

4.2.3 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 after the previous injection.

4.2.4 Deferral of Injections Due to Pregnancy

Female study participants of child-bearing age must be questioned regarding the possibility of pregnancy prior to each injection. In the event of pregnancy, study injections must be discontinued during the pregnancy and any post-partum period of breastfeeding.

4.2.5 Non-Study Eye Injections

If the non-study eye is going to be treated for any condition which requires treatment with an anti-VEGF agent, study provided aflibercept must be used. However, if intravitreous treatment is planned on the same day as an intravitreous injection in the study eye, the study eye will be injected first, followed by the non-study eye (see Procedures Manual for additional details). If a non-study anti-VEGF medication is desired to be administered by intravitreous injection in the non-study eye, a discussion with the Protocol Chair is required first.

4.3 Aflibercept Group Follow-Up Treatment

4.3.1 Retreatment with Intravitreous Injections of Aflibercept for Vitreous Hemorrhage and underlying PDR

All eyes will receive an injection of aflibercept at the 4-week, 8-week and 12-week visits, unless an adverse event precludes treatment.

Starting at the 16-week visit, eyes with no contraindication to additional aflibercept injections will be evaluated for retreatment based on the status of the hemorrhage and neovascularization. In general, the eye will receive an injection at each treatment assessment visit unless <u>one</u> of the below criteria is met:

1. Success: the vitreous hemorrhage has sufficiently cleared such that there is an adequate view of the entire fundus and neovascularization is absent
   - Injection is deferred.
2. Stability: it has been at least 24 weeks since the initial injection, the eye has received at least 2 prior consecutive injections, and the size and density of the hemorrhage and any neovascularization is clinically unchanged since the last visit.
   - Injection is deferred.
3. A vitrectomy has already been performed
   - Eyes in the aflibercept group that receive vitrectomy will follow the intra- and post-operative anti-VEGF treatment regimen described in sections 4.4 and 4.5.2 for the Vitrectomy Group.

4.3.2 PRP during Follow-Up

PRP must not be given unless failure criteria are met (see below for cases that first require discussion with the Protocol Chair or Coordinating Center designee). In addition, if any future treatment with aflibercept 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.

- *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 than when first adequately visualized 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.*

4.3.3 Vitrectomy during Follow-Up

Vitrectomy may be performed in the aflibercept group according to the criteria below. See section 4.4 regarding the vitrectomy procedure. Eyes in the aflibercept group that undergo vitrectomy must also receive intraoperative PRP until "complete".

4.3.3.1 Prior to 16 Weeks

Vitrectomy prior to 16 weeks should not be performed unless one of the following is present:

- Traction retinal detachment involving (within 1 disc diameter) or actively threatening the macula
- Rhegmatogenous retinal detachment
- Neovascular glaucoma resulting in increased intraocular pressure that cannot be controlled medically, angle neovascularization, or progressive neovascularization of the iris (at least 2 clock hours)
- Ghost cell glaucoma resulting in increased intraocular pressure that cannot be controlled medically

If other circumstances develop for which vitrectomy is being considered prior to 16 weeks, the Protocol Chair will be contacted for approval.

4.3.3.2 At and After 16 weeks

After the 16 week visit, vitrectomy may be performed (but is not required) if there is 1) persistent vitreous hemorrhage causing vision impairment and 2) the eye has received at least 2 consecutive prior injections. However, if this is the 3rd or more time the hemorrhage recurred after a period of clearance during the study, vitrectomy may be performed at investigator discretion without first performing 2 additional injections.

If the investigator believes vitrectomy is required for the safety of the participant and the study eye does not meet these criteria, protocol chair approval is required to proceed.

4.4 Vitrectomy

For study eyes receiving vitrectomy, vitrectomy will be performed according to the investigator's usual routine, including pre-operative care, surgical procedure, and post-operative care. However, a 23 or smaller gauge vitrectomy system must be used (20 gauge is not permitted).

Optional additional procedures at the discretion of the investigator include, but are not limited to:

- Removal of the internal limiting membrane.
- Use of agents to improve visualization of membranes, (e.g. triamcinolone acetonide, indocyanine green dye, or other staining agents).

- Use of corticosteroids (intravitreous, sub-tenon's, sub-conjunctival) at the close of the procedure.
- Cataract extraction.

Study intravitreous aflibercept may be given pre-operatively, but then should not be given thereafter unless there is recurrent hemorrhage (see section 4.5.2 below). If pre-op aflibercept is given, it is strongly recommended that it be given between 1 day to 1 week prior to the procedure, although it can be administered up to 2 weeks prior if necessary.

4.4.1 Vitreous and Aqueous Sample Collection

Participation in the ancillary sample collection component is not a requirement for participation in this study. It is expected that sites with the capability to obtain and ship intraocular fluids will participate. At the time of consent into the main study, participants will have the option of signing the ancillary sample collection portion of the informed consent form to indicate their willingness to provide either a vitreous sample only (at least 1 cc of undiluted vitreous collected during the vitrectomy procedure) or to provide both vitreous and an additional aqueous sample (requiring an additional anterior paracentesis to collect at least 0.1 cc of aqueous fluid).

If consent for vitreous and/or aqueous sampling is obtained, the sample(s) will be collected and shipped on dry ice to a central laboratory for storage until analyses are completed. Details regarding collection, sample labeling, storage, and shipment can be found in the ancillary study procedures manual.

4.4.2 Deferral or Cancellation of Surgery in the Vitrectomy Group

Surgery may be cancelled if there is substantial improvement in vitreous hemorrhage such that visual acuity is no longer affected.

If surgery is postponed for reasons other than substantial vitreous hemorrhage improvement, it should be re-scheduled as soon as possible.

Whether surgery is deferred or cancelled, protocol follow-up visits will continue as scheduled based on time from randomization.

4.5 Vitrectomy Group Intra- and Post-Operative Treatment

4.5.1 Panretinal Photocoagulation in the Vitrectomy Group

PRP should be placed to the extent that it is considered "complete". "Complete" PRP is defined as 500 micron size burns on the retina placed no further than 1 to 2 burn widths apart beginning ~3000 microns from the macular center and extending at least to the equator for 12 clock hours. See procedures manual for additional details, including use of automated pattern.

If it is determined during surgery that the eye has already received "complete" PRP, further PRP treatment is not required. PRP treatment can be performed using the investigator's standard procedure and may include indirect delivery.

If the size or amount of neovascularization increases following completion of the initial PRP session, additional PRP should be given if possible. Aflibercept may be given for neovascularization in the absence of recurrent hemorrhage after discussion with the protocol chair (see below for treatment of recurrent hemorrhage from NV).

4.5.2 Treatment for Recurrent Vitreous Hemorrhage in the Vitrectomy Group

If there is recurrent hemorrhage, no treatment should be given within the first 4 weeks post-vitrectomy. After 4 weeks, if the investigator determines there is recurrent hemorrhage from neovascularization, two injections of study aflibercept will be given, 4(±1) weeks apart. Additional aflibercept may be given every 4(±1) weeks thereafter, at the discretion of the investigator. Repeat vitrectomy (or air/fluid exchange) may only be performed if the recurrent hemorrhage has not cleared after at least 2 consecutive 4-week injections. Otherwise, protocol chair approval is required to re-operate.

4.6 Cataract Surgery (Both Groups)

Investigators should evaluate lens changes throughout the course of follow-up and consider cataract surgery (or referral for possible cataract surgery) when a lens change is thought to be visually significant based on the investigator's judgment. If the visual potential of the study eye is unknown, the investigator should assume that there is potential for clinically relevant improvement in vision. Cataract surgery may be performed as part of the surgeon's usual routine. Limited data will be collected for the study.

4.7 Treatment for Diabetic Macular Edema (Both Groups)

No anti-VEGF should be given for DME within 6 weeks of the initial randomized treatment. For post-surgical edema, steroid drops or other alternatives may be given at the discretion of the investigator. After 6 weeks, if DME is present (OCT CSF above gender and OCT machine-specific thresholds and investigator has confirmed thickening is due to diabetic macular edema and not post-surgical macular edema or other cause) and vision is 20/32 or worse, treatment with intravitreous aflibercept and deferred focal/grid laser will be given, using the DRCR.net intravitreous anti-VEGF retreatment protocol (section 4.7.1 below).

For eyes with DME and best-corrected visual acuity better than 20/32, protocol chair approval is required to initiate anti-VEGF treatment. Once initiated, the DRCR.net intravitreous anti-VEGF retreatment protocol regimen must be followed.

4.7.1. Intravitreous Injection Retreatment for DME

Once aflibercept treatment has been initiated for DME, the eye will be evaluated at each visit for retreatment. In general, an eye will continue to receive an injection if the eye is improving or worsening on OCT or visual acuity. The first time an eye has not improved or worsened the eye will receive an injection. If the eye has not improved or worsened for at least 2 consecutive 4-week injections and the OCT CSF thickness is less than the gender specific spectral domain OCT threshold (see below) and visual acuity is 20/20 or better, then injection will be deferred. If the eye has not improved or worsened for at least 2 consecutive 4-week visits and the OCT CSF thickness is ≥ the gender specific spectral domain OCT threshold or visual acuity is worse than 20/20, the following will be done:

- If less than 24 weeks from the initial injection for DME, an injection will be given.
- At and after 24 weeks, the injection will be deferred.

The protocol chair or designee must be contacted prior to deviation from the injection protocol. See the DRCR.net Procedure Manual for additional details.

Spectral domain OCT central subfield gender-specific threshold:

- Zeiss Cirrus: 290 microns in women, and 305 microns in men
- Heidelberg Spectralis: 305 microns in women, and 320 microns in men

4.7.2. Focal/Grid Laser Treatment for DME

In general, focal/grid laser will be initiated at or after 24 weeks from the initial injection for DME if 1) the OCT central subfield thickness is greater than the OCT central subfield gender-specific threshold (above) or there is edema that is threatening the fovea and 2) the eye has not improved on OCT or visual acuity from the last two consecutive injections. Once focal/grid laser has been initiated, retreatment with focal/grid laser will be given unless one of the following is present: 1) focal/grid laser has been given in the previous 13 weeks, 2) complete focal/grid laser has already been given in the investigator's judgment, 3) the OCT central subfield thickness is less than the OCT central subfield gender-specific threshold (above) and there is no edema threatening the fovea, 4) the eye has improved since the last laser treatment. The protocol chair or designee must be contacted prior to deviating from the focal/grid laser protocol. See the DRCR.net Procedure Manual for additional details.

CHAPTER 5.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

5.1 Endophthalmitis

Diagnosis of endophthalmitis following intravitreous injections is based on investigator's judgment. A culture is required prior to initiating antibiotic treatment for presumed endophthalmitis.

5.2 Treatment of Diabetic Retinopathy in Non-study Eye

Treatment of diabetic retinopathy, including DME, in the non-study eye is at investigator discretion. However, if anti-VEGF treatment will be given in the non-study eye, study aflibercept must be used.

5.3 Use of Intravitreal Anti-VEGF for Conditions Other than DME in the Study Eye

If an ocular condition other than DME or DR develops in the study eye for which aflibercept is an FDA approved treatment (e.g. neovascular AMD, macular edema following central retinal vein occlusion), the use of study aflibercept is at the discretion of the investigator. Any off-label use of anti-VEGF in the study eye for an ocular condition other than DR, will require discussion with and approval by the protocol chair or designee. Study aflibercept must be used for any anti-VEGF treatment in the study eye.

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 a study participant 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 him or her.

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, and approximately every six months thereafter. 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 participant-oriented newsletter may be sent 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 participants.

5.8 Study Participant Reimbursement

The study will be providing the study participant with a $25 merchandise or money card per completed protocol visit. Additional travel expenses may be paid in cases for participants with higher expenses. In situations of financial hardship supplemental funds for patient expenses may be available on a case by case basis.

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.

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 participant, 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 (including treatment of the non-study eye with study 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 participant'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 DRCR.net 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 or 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 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. If the study participant required hospitalization, the hospital discharge summary must also be sent to the Coordinating Center.

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 reporting serious study-related adverse events and abiding by any other reporting requirements specific to their Institutional Review Board.

6.4 Data and Safety Monitoring Committee Review of Adverse Events

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

6.5 Risks

6.5.1 Potential Adverse Effects of Aflibercept

The most common adverse reactions (≥5%) reported in patients receiving aflibercept were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, vitreous detachment, and vitreous floaters.

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with aflibercept including endophthalmitis and retinal detachment.

Safety data specific to the diabetes population were published from phase III studies VISTA and VIVID, which included 872 eyes with DME with central involvement that received either intravitreal aflibercept every 4 weeks, intravitreal aflibercept every 8 weeks after 5 initial monthly doses, or macular laser photocoagulation. Overall, the incidences of ocular and non-ocular adverse events were similar across treatment groups at 52 weeks.[32] The incidence of APTC-defined thromboembolic events was similar across treatment groups. There were no reported cases of endophthalmitis, and intraocular inflammation occurred in less than 1% of injections. Through 100 weeks, an integrated safety analysis found that the most frequent serious ocular adverse event was cataract (2.4% and 1.0% in the aflibercept groups compared with 0.3% in the laser group).[33] The incidence of APTC ATEs in VISTA and VIVID during the 100 weeks study duration was 6.4% (37out of 578) in the combined EYLEA groups compared with 4.2% (12 out of 287) in the control group.[33]

There may be side effects and discomforts that are not yet known.

6.5.2 Potential Adverse Effects of Intravitreous Injection

Rarely, the drugs used to anesthetize the eye before the injections (proparacaine, tetracaine, or xylocaine) can cause an allergic reaction, seizures, and an irregular heartbeat less than 1% of the time.

Sub-conjunctival hemorrhage or floaters will commonly occur as a result of the intravitreous injection. Mild discomfort, ocular hyperemia, increased lacrimation, discharge or itching lasting for up to a few days is also likely (more than 10% of the time).

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 intravitreous 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 Vitrectomy

6.5.3.1 Anesthesia

Anesthesia may be general endotracheal or local retrobulbar/peribulbar, usually with systemic sedation. Risks of systemic sedation and general anesthesia include cardiac arrhythmia and death. The risks of retrobulbar/peribulbar anesthesia include: retrobulbar hemorrhage; perforation of the eye by the needle; damage to the optic nerve; double vision lasting up to 24 hours or more; drooping of the eye lid 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 epileptic fits, drowsiness, confusion, loss of verbalization, convulsions, respiratory arrest, or cardiac arrest.

6.5.3.2 Surgical Procedure

Risks of the vitrectomy procedure include a retinal tear (5%) and retinal detachment (1%). Uncommon risks include infection (1/5,000) and serious hemorrhage (1/5,000). Very rare risks include visual field defect, visual loss due to macular toxicity of light or dye (if used) or manipulation, and optic neuropathy. In phakic eyes, cataract progression is likely.

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 very rare risk of an allergic response to the topical medications used to anesthetize the eye or dilate the pupil that occurs in less than 1% of eyes. Dilating drops rarely could cause an acute angle closure glaucoma attack (less than 1 in 1000)[35], but this is highly unlikely since the participants in the study will have had their pupils dilated many times previously.

There are no known risks associated with OCT.

CHAPTER 7.
STATISTICAL METHODS

The approach to sample size and statistical analysis is summarized below.

7.1 Sample Size

The sample size has been chosen for the primary study objective, which is to compare visual acuity outcomes over time of prompt vitrectomy + PRP regimen versus intravitreous aflibercept regimen in eyes with vitreous hemorrhage from PDR for which intervention is deemed necessary. The primary outcome is visual acuity area under the curve (AUC) from baseline to 24 weeks. The resulting analysis is a treatment group comparison of mean AUC adjusting for baseline visual acuity and baseline lens status.

7.1.1 Sample Size Assumptions

Aflibercept Group: To provide estimates for the aflibercept arm, data from the DRCR.net Protocol N trial (An Evaluation of Intravitreal Ranibizumab for Vitreous Hemorrhage Due to Proliferative Diabetic Retinopathy) were reviewed for eyes with baseline visual acuity 20/32 or worse. Eyes in Protocol N had structured treatment through 16 weeks and visits at 4, 8, and 12 weeks. Treatment was at investigator discretion between 16 and 52 weeks, at which time visual acuity was measured. Based on visual acuity data (Table 1), the standard deviation of the AUC at 12 weeks was 19.2 (95% CI 17.1, 22.0) and the correlation with baseline visual acuity was -0.39 (95% CI -0.53, -0.23). Assuming a true standard deviation of 19.2, this adjustment yields an effective standard deviation of 17.7 (95% CI 16.3 to 18.7).

Table 1. Visual acuity data from eyes in the ranibizumab group of Protocol N with baseline visual acuity 20/32 or worse. Visits in common with this protocol are in boldface.

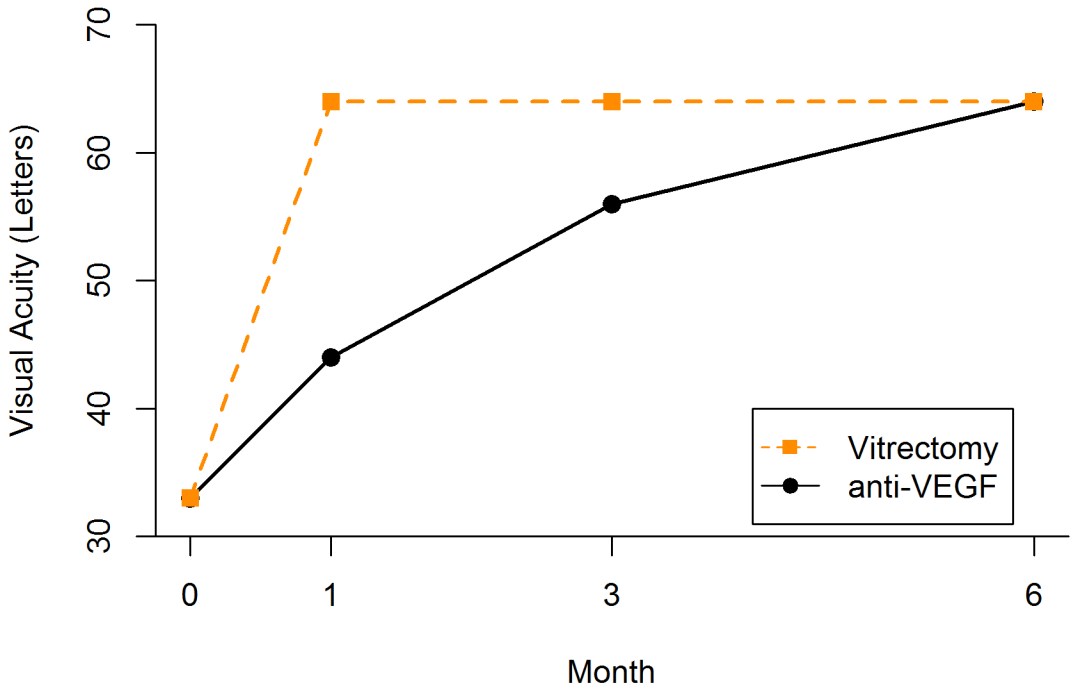
Visit	Mean	SD
Baseline	**33**	**28**
4-week	**44**	**29**
8-week	50	29
12-week	**56**	**27**
52-week	64	22

Vitrectomy Group: For the vitrectomy arm, data from a randomized trial comparing vitrectomy with and without bevacizumab for proliferative diabetic retinopathy were reviewed (Manabe et al., 2015).[36] In the sham group, mean baseline visual acuity was 1.14 logMAR (28 letters) and 30 of the 34 participants (88%) were enrolled to treat persistent vitreous hemorrhage. At one month after surgery, mean visual acuity improved to 0.43 logMAR (64 letters). Without participant-level data, the standard deviation of the AUC cannot be estimated. However, the standard deviation of visual acuity at one month was 0.48 logMAR (24 letters), which is less than the 29 letter standard deviation for visual acuity observed in the ranibizumab group at 4 weeks in Protocol N (Table 1). Therefore, assuming the standard deviation of AUC for this group is similar to the anti-VEGF group is likely a conservative approach.

Projected Difference: The estimated treatment group difference in AUC at 24 weeks (6 months) was calculated using the above data, assuming that both groups have baseline visual acuity of 33 letters, and the aflibercept arm reaches a visual acuity of 64 letters by 6 months (Figure 1). These

calculations projected an AUC difference of +8.3 letters in favor the of the vitrectomy arm. If visual acuity in the aflibercept arm did not reach 64 letters until 1 year, and had a visual acuity of only 60 letters at 6 months, the difference would be +9.3 letters.

Figure 1. Projected trajectories of visual acuity in the aflibercept and vitrectomy arms.



7.1.2 Sample Size Estimation

Table 2 shows sample sizes estimates under several scenarios. The final sample size has been computed with type 1 error rate of 0.049 (0.001 adjustment for DSMC review) and 80% power. Assuming an effective standard deviation of 18 (after adjusting for correlation between baseline and outcome), and a true difference in mean AUC of 8 letters, the required total sample size is 162 eyes. This will be increased to 200 eyes to account for uncertainty in our projections and loss to follow-up; if the rate of loss to follow-up is 7.5%, then the power for an effective sample size of 185 would be 85%.

Table 2. Sample size estimates for a range of true mean differences and effective standard deviations (after adjustment for correlation between baseline and outcome). Total number of eyes required for 80% / 90% power are shown in cells. The type I error rate is 0.049.

Power: 80% / 90%	*Effective Standard Deviation*		
True Mean Difference	**17**	**18**	**19**
7	190 / 252	212 / 282	236 / 314
8	146 / 194	162 / 216	182 / 242
9	116 / 154	130 / 172	144 / 192

7.1.3 Statistical Power

As there are several binary variables of interest as secondary outcomes (Section 7.3), confidence interval half-widths (Table 3) and statistical power (Table 4) for the difference of two percentages have been calculated based on an effective total sample size of 186 eyes (200 eyes enrolled with 7% loss to follow-up). In Protocol N, among eyes in the ranibizumab group with baseline visual acuity of 20/32 or worse, 37% achieved 20/32 vision or greater by one year. As power for the difference of two percentages is dependent upon the absolute value of the percentages, this estimate is used as a starting point for the calculations below.

Table 3. Expected half-widths of a 95% confidence interval for the difference of two percentages (effective sample size of 186). The width depends upon the true percentages.

Outcome Rate	*Difference in Group B*		
in Group A	**+10%**	**+15%**	**+20%**
10%	10%	11%	11%
30%	14%	14%	14%
50%	14%	14%	14%

Table 4. Power for the comparison of two percentages (effective sample size of 186). The power depends upon the true percentages.

Outcome Rate	*Difference in Group B*		
in Group A	**+10%**	**+15%**	**+20%**
10%	41%	72%	91%
30%	25%	50%	76%
50%	23%	49%	76%

The expected half-widths for a within-group binary 95% confidence interval (e.g., percentage of eyes in aflibercept group requiring vitrectomy) are shown in Table 5. The expected half-widths for a 95% confidence interval of a difference of means (e.g., visual acuity letter score) are shown in Table 6.

Table 5. Expected half-widths of a 95% confidence interval for a within-group binary outcome (effective sample size of 93). The half-width depends upon the true outcome rate.

Outcome Rate		
10%	**30%**	**50%**
6%	9%	10%

Table 6. Expected half-widths of a 95% confidence interval for a between-group difference of means (effective sample size of 186). The half-width depends upon the common standard deviation.

Standard Deviation		
15	**20**	**25**
4.3	5.7	7.2

7.2 Primary Analysis Plan

7.2.1 Principles for Analysis

The primary analysis will consist of a treatment group comparison of mean visual acuity AUC from baseline to 24 weeks between the two treatment groups adjusting for baseline visual acuity and phakic status using analysis of covariance. Only baseline and outcome visits (4, 12, 24, 36, 52, 68, 84, and 104 weeks), which are common to both groups, will be used to calculate AUC through the appropriate visit for the primary and secondary outcomes (e.g., 24 weeks for primary outcome). AUC will be calculated for each participant by the trapezoidal rule using the following formula:

$$AUC = \sum_{i=1}^{n} \left(\frac{V_i + V_{i+1}}{2} \times d \right)$$

Where V_i is the visual acuity from baseline measured at the i^{th} visit, d is the number of days between visits i and $i+1$, and n is the number of outcome visits included in the analysis. For example, the primary outcome has $n = 4$ as the analysis will include visits at baseline, 4 weeks, 12 weeks, and 24 weeks. For presentation, AUC will be divided by the number of days between baseline and the n^{th} visit so that the value shown will have units of letters rather than letter·days. This statistic can then be interpreted as the average visual acuity over the time period between baseline and the n^{th} visit.

The primary analysis will include all randomized eyes according to treatment group assignment at randomization. Rubin's multiple imputation will be used to handle missing data. A sensitivity analysis using only observed data will also be conducted. If the analyses of imputed and observed data differ substantially, then exploratory analyses will be performed to evaluate factors that may have contributed to the differences.

Pre-planned subgroup analyses will be described in the detailed Statistical Analysis Plan and include analyses by history of PRP, treatment for DME, and phakic 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 the primary analysis by including factors potentially associated with the outcome for which there is an imbalance between groups.

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.

The primary outcome was primarily selected for sample size considerations. The long-term additional key outcomes and within-group outcomes will be equally important as the area under the curve outcome for evaluating the overall follow-up course for these two treatment approaches. Therefore, publication is not planned until the full 104 week follow-up has closed.

7.2.2 Per-Protocol Analysis

A per-protocol analysis will be conducted that will include all randomized eyes except those in the prompt vitrectomy + PRP group that never receive vitrectomy and eyes from the aflibercept group that missed an injection. The intent-to-treat analysis is considered the primary analysis. If

the results of the primary and per-protocol analyses differ substantially, then exploratory analyses will be performed to evaluate the factors that have contributed to the differences.

7.2.3 Interim Analysis Plan

There is no formal interim data monitoring for efficacy or futility planned.

7.3 Secondary Outcomes

Additional analyses of visual acuity and other outcomes are summarized in the table below. Analyses will include adjustments for baseline visual acuity and phakic status. Analyses will be conducted at 24, 52, and 104 weeks (note that visual acuity AUC at 24 weeks is the primary outcome, not a secondary outcome). In addition, mean visual acuity, visual acuity AUC, and percentage of eyes with various visual acuity cutoffs will also be compared at the 4 and 12 week visits as the between-group difference in vision is expected to be greatest during the first months of the trial.

Table 3. Analyses of Secondary Outcomes.

Outcome	Analysis Technique
Mean visual acuity and AUC	Analysis of covariance
Percentage of eyes ≥ 20/20, 20/32, or 20/40, ≤ 20/200 and ≤ 20/800	Binomial regression
Percentage of eyes with recurrent vitreous hemorrhage on clinical exam	Binomial regression
Percentage of eyes with retinal neovascularization	Binomial regression
OCT central subfield thickness	Analysis of covariance*†

*No adjustment for visual acuity.
†No adjustment for baseline central subfield thickness as vitreous hemorrhage will prevent obtaining usable scans for many participants.

7.3.1 Outcomes within Treatment Groups

Within each treatment group, the following outcomes and their 95% confidence intervals will be tabulated:

- Percentage of eyes undergoing vitrectomy (initial vitrectomy in aflibercept group and repeat vitrectomy in vitrectomy group)
- Number of intravitreous aflibercept injections performed
- Percentage of eyes receiving PRP (aflibercept group only)

7.3.2 Economic Analysis

The purpose of the economic analysis is to compare the treatment groups with respect to cost, cost-effectiveness and workplace productivity loss. The analysis plan is briefly described and will be detailed in a separate document.

Data from the clinical trial on number of clinic visits completed, number of procedures performed (e.g. vitrectomy, OCT, exam), and number of study aflibercept injections 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 percent productivity loss for each treatment arm will be incorporated into the analysis.

Scores from the WPAIQ, administered at baseline, 4, 12, 24, 52, and 104 weeks, will be analyzed by treatment group using analysis of covariance to adjust for baseline score and phakic status. Adjusted 95% confidence intervals for treatment group differences will be calculated. Mean change at each visit in the following four scores will be analyzed:

- Absenteeism: percent work time missed due to vision
- Presenteeism: percent impairment while working due to vision
- Work Productivity Loss: percent overall work impairment due to vision
    - Combination of absenteeism and presenteeism scores
- Activity Impairment: percent activity impairment due to vision

In addition, area under the curve analyses will be conducted using data from all available outcome visits for the Work Productivity Loss and Activity Impairment scores.

7.4 Safety Analysis Plan

Adverse events will be categorized as systemic, study eye, or non-study eye. The events will be tabulated by treatment group. As only one study eye shall be enrolled, there is no group of patients with two study eyes, which would need to be tabulated separately. The frequency of the event occurring at least once will be calculated. Rates of adverse events will be compared between treatment groups using Barnard's unconditional exact test.

The following ocular adverse events will be assessed:

- Endophthalmitis
- Any retinal detachment
- Rhegmatogenous retinal detachment
- Tractional retinal detachment
- Retinal tear
- Ocular inflammation (defined as anterior chamber cell, anterior chamber flare, choroiditis, episcleritis, uveitis, iritis, or vitreal cells)
- Adverse intraocular pressure (IOP) events
    - Increase in IOP $\geq$ 10 mmHg from baseline
    - IOP $\geq$ 30 mmHg
    - Initiation of medication to lower IOP that was not in use at baseline
    - Glaucoma surgery
- Neovascularization of the iris
- Cataract extraction in eyes phakic at baseline
- Visually significant cataract on clinical exam

The following serious systemic adverse events will be assessed:

- Primary:
    - Death
    - Serious adverse event (at least one)
    - Hospitalization (at least one)

- Cardiovascular/cerebrovascular events according to Antiplatelet Trialists' Collaboration (excerpted from BMJ Jan 8, 1994):
    - Non-fatal myocardial infarction
    - Non-fatal stroke (counted only if symptoms lasted at least 24 hours)
    - Death attributed to cardiac, cerebral, hemorrhagic, embolic, other vascular (does not need to be ischemic in origin), or unknown cause
    - At least one event (non-fatal myocardial infarction, non-fatal stroke, or death attributed to potential vascular or unknown cause)

  APTC Notes: Transient ischemic attacks, angina, and possible myocardial infarction or stroke are not counted. 'Nonfatal' myocardial infarction or stroke required that the participant was alive at the end of the study. If not, only the death is counted.

- Secondary:
    - Frequency of at least one event per participant in each Medical Dictionary for Regulatory Activities (MedDRA) system organ class

An additional tabulation will be made for adverse events possibly related to study treatment.

7.5 Additional Tabulations and Analyses

The following will be tabulated according to treatment group:

- Baseline demographic and clinical characteristics
- Visit completion rate
- Treatment completion

7.6 Statistical Modeling Techniques

All model assumptions, including linearity, normality of residuals, and homoscedasticity will be verified where applicable. If model assumptions are not reasonably satisfied, then a transformation, nonparametric analysis, or other appropriate approach will be considered.

CHAPTER 8. REFERENCES

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