# Diabetic Retinopathy Clinical Research Network

# Randomized Trial of Intravitreous Aflibercept versus Intravitreous Bevacizumab + Deferred Aflibercept for Treatment of Central-Involved Diabetic Macular Edema

**Version 4.0**

**June 28, 2021**

## Contact Information

**Coordinating Center**
Director: Adam R. Glassman, M.S.
Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647
Phone: 813-975-8690
Fax: 800-816-7601
Email: aglassman@jaeb.org

**Protocol Co-Chairs**

**Chirag Jhaveri, MD**
Retina Research Center
3705 Medical Parkway Suite 420
Austin, TX 78705
Phone: 512-454-5851
Email: cjhaveri@e-retina.net

**Frederick L. Ferris III, MD**
National Eye Institute
BG 10-CRC RM 3-2531
10 CENTER DR
BETHESDA MD 20814
Phone: 301-496-5248
Email: frederick.ferris@nih.gov

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# CHAPTER 1
# BACKGROUND INFORMATION AND STUDY SYNOPSIS

## 1.1 Background Information

### 1.1.1 Diabetic Retinopathy Complications and Public Health Impact

The age-adjusted incidence of diabetes mellitus in the United States has reportedly doubled in recent history.[1] Estimates suggest that by the year 2035, approximately 592 million individuals worldwide will be affected by this chronic disease.[2] The increasing global epidemic of diabetes implies an increase in rates of associated vascular complications from diabetes. At present at least 5 million people over the age of 40 in the United States are estimated to have diabetic retinopathy (DR) in the absence of diabetic macular edema (DME), and an additional 800,000 have DME, according to data from the Centers for Disease Control.[3] Despite advances in diagnosis and management of ocular disease in patients with diabetes, eye complications from diabetes mellitus continue to be a leading cause of vision loss and new onset blindness in working-age individuals throughout the United States.[4, 5]

### 1.1.2 DME and Its Treatment

DME is manifestation of diabetic retinopathy that produces loss of central vision. DME is currently a leading cause of moderate vision loss in patients with diabetes.[6] Without intervention, 33% of 221 eyes in the Early Treatment Diabetic Retinopathy Study (ETDRS) with center-involved DME (CI-DME) experienced "moderate visual loss" (defined as a 15 or more letter score decrease in visual acuity) over a 3 year period.[7] The Diabetic Retinopathy Clinical Research Network (DRCR.net) study "Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination with Laser Photocoagulation for Diabetic Macular Edema" (Protocol I) indicated that treatment for DME with intravitreous anti-VEGF therapy (0.5 mg ranibizumab) with prompt or deferred focal/grid laser provides visual acuity outcomes at 1 year and 2 years that are superior to focal/grid laser alone or focal/grid laser combined with intravitreous corticosteroids.[8] Results of that study provided definitive confirmation of the important role of vascular endothelial growth factor (VEGF) in DME and the superiority of anti-VEGF agents in the treatment of DME. Additional phase 3 studies have since confirmed the superiority of anti-VEGF agents to manage DME.[9-11]

### 1.1.3 Rationale for Comparing Aflibercept to Bevacizumab + Deferred Aflibercept

Three anti-VEGF agents, aflibercept, bevacizumab, and ranibizumab, have been shown to be effective for treatment of diabetic macular edema. Based on results from DRCR.net Protocol T, when visual acuity loss is relatively mild, there are not meaningful differences in visual acuity outcomes, on average, among the three agents. However, at worse levels of visual acuity, aflibercept is more effective at improving vision than the other 2 agents at 1 year and more effective at improving vision than bevacizumab at 2 years. There are considerable cost differences among aflibercept ($1961/dose), bevacizumab (current Medicare allowable charge: $67/dose), and 0.3-mg ranibizumab ($1189/dose).

In Protocol T, although aflibercept treatment in Protocol T resulted in better visual acuity outcomes for eyes with worse levels of visual acuity, bevacizumab was effective for many eyes and a cost-effectiveness analysis showed that bevacizumab was more cost effective than aflibercept.[12] The cost difference between aflibercept and bevacizumab might limit availability

of aflibercept for some patients. According to the 2016 ASRS PAT Survey, approximately 50% of United States retinal specialist indicated that insurance requires use of bevacizumab as the first line treatment for at least some of their patients. In the subgroup of Protocol T eyes with baseline visual acuity of 20/50 or worse, 60% of bevacizumab treated eyes had a 10 or more letter improvement and 41% had a 15 or more letter improvement at 1 year. At 2 years, 66% of eyes with worse baseline visual acuity had a 10 or more letter improvement and 52% had a 15 or more letter improvement.[13] Thus, many eyes initially treated with bevacizumab for DME might gain enough vision with bevacizumab therapy that they might not derive greater benefit if given another anti-VEGF agent such as aflibercept. Many clinicians initiate treatment with bevacizumab for patients with decreased visual acuity from DME (61% of PAT Survey respondents start with bevacizumab for decreased visual acuity from DME). However, there is no scientific evidence that this treatment strategy of switching treatment from bevacizumab to aflibercept among eyes not improving is as effective at improving vision as initiating treatment with aflibercept. It is unknown if this approach ultimately has deleterious effects on visual acuity compared with starting with aflibercept.

Given this, a study assessing a switch from bevacizumab to aflibercept only in cases in which bevacizumab was not judged to be successful is perceived to be of great public health interest.

### 1.1.4 Summary of Previous Research of Switching Anti-VEGF Agents

Both aflibercept and bevacizumab have been shown to improve vision in eyes with DME. In eyes with DME and at least moderate vision loss, both aflibercept and bevacizumab were also shown to be successful in many eyes. However, aflibercept was shown to be more effective at improving vision, on average, at 1 year and at 2 years. Due to the large cost difference between the two drugs, many clinicians and patients are choosing to initiate treatment with bevacizumab and then switch to aflibercept depending on the eye's response to bevacizumab treatment. However, there is no scientific evidence that this treatment strategy is as effective at improving vision as initiating treatment with aflibercept. Patients and clinicians do not know if this approach ultimately has deleterious effects on visual acuity. If starting with aflibercept is not better than starting with bevacizumab and switching to aflibercept if needed, the potential cost savings to future patients and the health care system would be substantial. However, if starting with aflibercept is better, then patients, clinicians, and health care providers can make informed decisions for how to best treat patients with DME and at least moderate vision loss.

## 1.2 Study Objectives

To compare the efficacy of intravitreous aflibercept with intravitreous bevacizumab + deferred aflibercept if needed in eyes with CI DME and moderate vision loss.

## 1.3 Study Design and Synopsis of Protocol

### A. Study Design

- Randomized, multi-center clinical trial.

### B. Major Eligibility Criteria

- Age ≥18 years.
- Type 1 or type 2 diabetes
- The study eye must meet the following criteria:
    - Visual acuity (VA) letter score in the study eye < 69 and ≥ 24 (approximate Snellen equivalent 20/50 to 20/320)
    - Ophthalmoscopic evidence of center-involved DME (i.e., involving the center of the macula)
    - Center-involved macular thickening on optical coherence tomography (OCT)
        - Zeiss Cirrus central subfield (CSF): ≥290µm in women or ≥ 305µm in men
        - Heidelberg Spectralis central subfield: ≥ 305µm in women or ≥320µm in men
    - No history of anti-VEGF treatment for DME in the past 12 months in the study eye and no history of any other treatment for DME in the study eye in the past 4 months (such as focal/grid macular photocoagulation, intravitreous or peribulbar corticosteroids)
        - Enrollment will be limited to a maximum of 25% of the planned sample size with any history of anti-VEGF treatment for DME in the study eye. Once this number of eyes has been enrolled, any history of anti-VEGF treatment for DME in the study eye will be an exclusion criterion.
    - No history of major ocular surgery in the study eye within prior 4 months or anticipated within the next 6 months following randomization

**C. Treatment Groups**

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

- 2.0 mg intravitreous aflibercept
- 1.25 mg intravitreous bevacizumab + deferred intravitreous 2.0 mg aflibercept if eye meets switch criteria

Study participants may have one or two study eyes, if both eyes are eligible at the time of randomization. Study participants with two study eyes will be randomized to receive aflibercept in one eye and bevacizumab + deferred aflibercept (if switch criteria is met) in the other eye. Further details on randomization are located in section 2.4.

**D. Sample Size**

A minimum of 312 eyes (260 participants assuming 20% have two study eyes) are expected to be enrolled into the randomized trial.

**E. Duration of Follow-up:** 2 years

**F. Follow-up and Treatment Schedule**

- Follow-up visits occur every 4 weeks up to the 1 year visit

- Study eyes in both groups will be evaluated for an injection at each study visit according to the same retreatment protocol (DRCR.net anti-VEGF retreatment algorithm).
- At 12, 16, and 20 weeks, study eyes in the bevacizumab treatment group that meet all of the following switch criteria will be switched to treatment with aflibercept
    - OCT CSF thickness ≥ machine and gender specific thresholds
        - Zeiss Cirrus: ≥290µm in women or ≥ 305µm in men
        - Heidelberg Spectralis: ≥ 305µm in women or ≥320µm in men
    - VA not improved at least 5 letters from the prior two visits
    - OCT CSF not improved at least 10% from the prior two visits
    - VA is 20/50 or worse
- At and after 24 weeks, study eyes in the bevacizumab treatment group (that have not already switched to aflibercept) that meet all of the following switch criteria will switch to aflibercept
    - OCT CSF thickness ≥ machine and gender specific thresholds
        - Zeiss Cirrus: ≥290µm in women or ≥ 305µm in men
        - Heidelberg Spectralis: ≥ 305µm in women or ≥320µm in men
    - VA not improved at least 5 letters from the prior two visits
    - OCT CSF not improved at least 10% from the prior two visits
    - VA is 20/32 or worse
- After 1 year, visits occur every 4 to 16 weeks depending on disease progression and treatment administered
- All participants will have follow-up visits at 1 and 2 years

## G. Primary Efficacy Outcomes

- The primary analysis is a treatment group comparison of mean change in visual acuity over 2 years, area under the curve (AUC) adjusted for baseline visual acuity.

## I. Main Safety Outcomes

Ocular: endophthalmitis, retinal detachment, traumatic cataract due to injection, vitreous hemorrhage, inflammation, neovascular glaucoma, iris neovascularization

Systemic: death, serious adverse event, hospitalization, Antiplatelet Trialists' Collaboration (APTC) events

## J. Schedule of Study Visits and Examination Procedures

| Visit | 0 | 4w-48w Visits Every 4 w | 52w | Between 52w-104w Visits Every 4-16w* | 104w |
|---|---|---|---|---|---|
| E-ETDRS Best Corrected Visual Acuity[a] | X | X | X | X | X |
| OCT[b] | X | X | X | X | X |
| Eye Exam[c] | X | X | X | X | X |
| Fundus Photography[d] | X | | X | | X |

| | | | | | |
|---|---|---|---|---|---|
| Blood pressure | X | | X | | X |
| Hemoglobin A1c[e] | X | | X | | X |

E-ETDRS, Electronic Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography

A medical history will be elicited at baseline and an updated history at each visit. Concomitant medications will be recorded at baseline and updated at each visit. Adverse events will be recorded at each visit.

[a]Both eyes at each visit; includes protocol refraction in study eye at each visit. Protocol refraction in nonstudy eye is only required at baseline, 52 week and 104 week 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.
[c]Both eyes at baseline, 52 weeks and 104 weeks; study eye only at all other follow-up visits. Includes slit lamp exam (including assessment of lens), measurement of intraocular pressure, and dilated ophthalmoscopy.
[d]Digital 7-fields, 4WF or UWF; study eye only.
[e]Does not need to be repeated if Hemoglobin A1c 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, OCT, photography, and Study procedures manuals) provide details of the examination procedures and intravitreous injection procedures.

Photographers, OCT technicians, and visual acuity testers, including refractionists, will be masked to treatment group at the annual visits. Study participants will be initially masked to their treatment group assignment, but may find out the identity of the drug from billing documents. Investigators and study coordinators 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 Subjects and Obtaining Informed Consent

A minimum of 312 eyes (260 participants assuming 20% have two study eyes) 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. In addition, participants will be required to watch a short informational video about the trial and answer a few short questions to confirm understanding of the study. 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. 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.

## 2.2 Study Participant Eligibility Criteria

### 2.2.1 Participant-level Criteria

Inclusion

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

1. Age ≥ 18 years
   - *Individuals <18 years old are not being included because DME is so rare in this age group that the diagnosis of DME may be questionable.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes*
     - *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes*
     - *Documented diabetes by ADA and/or WHO criteria (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 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 four months, initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next four 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 at the time of study entry.
   - *Note: study participants cannot receive another investigational drug while participating in the study.*
8. Known allergy to any component of the study drug or any drug used in the injection prep (including povidone iodine prep).
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. Systemic anti-VEGF or pro-VEGF treatment within four months prior to randomization or anticipated use during the study.
    - *These drugs cannot be used during the study.*
11. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 24 months.
    - *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.*
12. Individual is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the next two years.

### 2.2.2 Study Eye Criteria

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

Study participants can have two study eyes only if both eyes 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. Best corrected E-ETDRS visual acuity letter score < 69 (i.e., 20/50 or worse) and ≥ 24 (i.e., 20/320 or better) within eight days of randomization.

b. On clinical exam, definite retinal thickening due to diabetic macular edema involving the center of the macula.

c. Diabetic macular edema present on OCT within eight days of randomization

- Zeiss Cirrus central subfield: ≥290µm in women or ≥ 305µm in men
- Heidelberg Spectralis central subfield: ≥ 305µm in women or ≥320µm in men
- *Investigator must verify accuracy of OCT scan by ensuring it is centered and of adequate quality*

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

Exclusions

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

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

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

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

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

i. History of an anti-VEGF treatment for DME in the past 12 months or history of any other treatment for DME at any time in the past four months (such as focal/grid macular photocoagulation, intravitreous or peribulbar corticosteroids).

- *Enrollment will be limited to a maximum of 25% of the planned sample size with any history of anti-VEGF treatment for DME. Once this number of eyes has been enrolled, any history of anti-VEGF treatment for DME will be an exclusion criterion.*

j. History of pan-retinal photocoagulation within four months prior to randomization or anticipated need for pan-retinal photocoagulation in the six months following randomization.

k. History of anti-VEGF treatment for a disease other than DME in the past 12 months.

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

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

n. Aphakia.

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

p. Evidence of uncontrolled glaucoma.

- *Intraocular pressure must be <30, with no more than one topical glaucoma medication, and no documented glaucomatous field loss for the eye to be eligible*
  - *Note – combination therapies are considered more than one medication*

## 2.3 Screening Evaluation and Baseline Testing

### 2.3.1 Historical Information

A 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 Visual Acuity-Refraction Testing Procedures Manual, OCT Procedures Manuals, Photography Testing Procedures Manual, and Study Procedures Manual. Visual acuity testing, ocular exam, fundus photography, and OCT 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. *(within eight days prior to randomization)*
   - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[14]
2. OCT on study eye *(within eight days prior to randomization)*
   - *For a given study participant, the same machine type should be used for the duration of the study, unless circumstances do not permit (e.g., replacement of damaged machine). If a switch is necessary, the same machine type should be used for the remainder of the study.*
3. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(within 21 days prior to randomization)*

4. Digital fundus photography in the study eye. *(within 21 days prior to randomization)*
5. Measurement of blood pressure *(see study procedures manual for collection procedure.)*
6. Laboratory Testing- Hemoglobin A1c
    - *Hemoglobin A1c does not need to be repeated if available in the prior three months. If not available at the time of randomization, the individual may be enrolled but the test must be obtained within three weeks after randomization.*

## 2.4 Enrollment/Randomization of Eligible Study Participants

Study participants can have two study eyes.

**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 injection must be given on the day of randomization; therefore, a study participant should not be randomized until this is possible. For study participants with two study eyes, it is strongly recommended that both eyes are treated on the day of randomization. If the investigator is not willing to perform bilateral injections on the same day, the second study eye must receive the injection within 7 days.

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

- Study participants with one study eye will be randomly assigned with equal probability stratified by site to receive either:
    - Group A: 2.0 mg intravitreous aflibercept
    - Group B: 1.25 mg intravitreous bevacizumab + deferred intravitreous 2.0 mg aflibercept if the eye meets switch criteria

- Study participants with two study eyes (both eyes eligible at time of randomization) will be randomized with equal probability to receive either:
    - Group A in the eye with greater visual acuity and Group B in the eye with lower visual acuity
    - Group B in the eye with greater visual acuity and Group A in the eye with lower visual acuity

  Note: if both eyes have the same visual acuity, the right eye will be considered the eye with greater visual acuity.

# CHAPTER 3
# TREATMENT REGIMENS

## 3.1 Introduction

The study eye is assigned to one of the two treatment groups.

The treatment groups are as follows:

- 2.0 mg intravitreous aflibercept
- 1.25 mg intravitreous bevacizumab + deferred intravitreous 2.0 mg aflibercept if the eye meets switch criteria

The initial injection will be given on the day of randomization. For study participants with two study eyes, it is strongly recommended that both eyes are treated on the day of randomization. If the investigator is not willing to perform bilateral injections on the same day, the second study eye must receive the injection within 7 days.

Treatment procedures are described below. The timing and criteria for retreatment are outlined in chapter 4.

## 3.2 Intravitreous Injections

### 3.2.1 Intravitreous Aflibercept Injection (Eylea)

Eylea® (intravitreous 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 assigned to receive aflibercept will receive a dose of 2.0 mg in 0.05 cc. Aflibercept will be obtained commercially by the clinical site. The physical, chemical, and pharmaceutical properties and formulation of aflibercept are provided in the Package Insert.

### 3.2.2 Bevacizumab (Avastin)

Bevacizumab (Avastin) is made by Genentech, Inc. and is approved by the FDA for the treatment of metastatic colorectal cancer as well as the treatment of non-squamous non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma.

Study eyes assigned to receive bevacizumab will receive a dose of 1.25 mg either obtained by the clinical site or provided by a single compounding pharmacy identified by the Network and distributed by the Network. The volume of the injection will be 0.05 cc. The physical, chemical, and pharmaceutical properties and formulation of bevacizumab are provided in the Clinical Investigator's Brochure.

### 3.2.3 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 protocol-specific study procedures manual.

### 3.2.4 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.

### 3.2.5 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 one 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 three weeks after the previous injection.

# CHAPTER 4
# FOLLOW-UP VISITS AND TREATMENT

## 4.1 Visit Schedule

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

First Year

- Visits every 4±1 weeks (with a minimum of 21 days between visits) through 1 year

Year 2

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

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

## 4.2 Testing Procedures

The following procedures will be performed at each protocol visit 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 the annual visits. Study participants will be initially masked to their treatment group assignment, but may find out the identity of the drug from billing documents. The investigators and the study coordinators will not be masked to the treatment group assignment.

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 the 1 and 2 year visits. When a refraction is not performed, the most-recently performed refraction is used for the testing.
2. OCT on the study eye
   - For a given study participant, the same machine type should be used for the duration of the study, unless circumstances do not permit (e.g., replacement of damaged machine). If a switch is necessary, the same machine type should be used for the remainder of the study.
3. Ocular exam on both eyes at the annual visits and study eye only at all other follow-up visits, including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy.
4. Digital fundus photography on the study eye only.
5. A blood pressure measurement will be collected at the annual visits.
6. Laboratory testing of Hemoglobin A1c at annual visits only.

- *HbA1c does not need to be repeated at annual visits if available in the prior 3 months.*

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.

## 4.3 Treatment During Follow Up

The treatment groups are as follows:

- 2.0 mg intravitreous aflibercept
- 1.25 mg intravitreous bevacizumab with deferred intravitreous 2.0 mg aflibercept if the eye meets switch criteria

### 4.3.1 Intravitreous Injection Re-Treatment

At the baseline visit all treatment groups will receive an intravitreous injection according to their assigned treatment group. After the initial injection each eye will be treated according to retreatment protocol. 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 injections and OCT CSF thickness is less than the gender-specific spectral domain OCT threshold (see below) and visual acuity is 20/20 or better, the injection will be deferred. If the eye has not improved or worsened for at least 2 consecutive visits and OCT CSF thickness is ≥ the gender-specific spectral domain OCT threshold or visual acuity is worse than 20/20, the following will be done:

- Prior to the 24-week visit, an injection will be given.
- At and after the 24-week visit, the injection will be deferred.

For study participants with two study eyes, if the re-treatment protocol determines that both eyes are to receive an intravitreous injection at the visit, it is strongly recommended that both eyes are treated on the same day. If the investigator is not willing to perform bilateral injections on the same day, the second study eye must receive the injection within 7 days.

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

Spectral domain OCT central subfield gender-specific thresholds:

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

### 4.3.2 Switch Criteria (Bevacizumab + Deferred Aflibercept group)

At the 12, 16 and 20 week visits, study eyes assigned to the bevacizumab + deferred aflibercept group will switch from bevacizumab injections to aflibercept injections when all of the following criteria have been met:

- OCT CSF thickness is above the following cutoffs:
  - Zeiss Cirrus CSF: ≥290µm in women or ≥ 305µm in men
  - Heidelberg Spectralis CSF: ≥ 305µm in women or ≥320µm in men
- VA not improved at least 5 letters from the prior two visits
- OCT CSF not improved at least 10% from the prior two visits
- Visual acuity is 20/50 or worse

Beginning at the 24 week visit through the end of the study, study eyes assigned to the bevacizumab + deferred aflibercept group that have not already switched to aflibercept will switch from bevacizumab injections to aflibercept injections when all the following criteria have been met*:*

- OCT CSF thickness is above the following cutoffs:
  - Zeiss Cirrus CSF: ≥290µm in women or ≥ 305µm in men
  - Heidelberg Spectralis CSF: ≥ 305µm in women or ≥320µm in men
- VA not improved at least 5 letters from the prior two visits
- OCT CSF not improved at least 10% from the prior two visits
- Visual acuity is 20/32 or worse

➢ *Note – If bevacizumab injections are deferred according to the criteria in section 4.3.1, and then the eye worsens, injections will resume using bevacizumab. Then, if the criteria above is met following two consecutive bevacizumab injections, the eye will switch to aflibercept.*

Eyes that meet the switch criteria will switch to aflibercept injections and receive 2 monthly injections of aflibercept, then continue with aflibercept injections through the end of the study according to the retreatment protocol described in section 4.3.1.

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

### 4.3.3 Failure Criteria

For study eyes in both treatment groups, when failure criteria is met, treatment is up to the investigator discretion.

At or after the 24 week visit, if <u>all</u> of the following criteria are met, the eye has met failure criteria and treatment is up to investigator discretion

- OCT CSF thickness ≥ eligibility machine and gender specific threshold
  - Zeiss Cirrus CSF: ≥290µm in women or ≥ 305µm in men
  - Heidelberg Spectralis CSF: ≥ 305µm in women or ≥320µm in men
- VA is 10 or more letters worse than baseline at 2 consecutive visits
- DME present on clinical exam that the investigator believes is the cause of the visual acuity loss
- There has been no improvement in VA (>5 letters) or OCT ( >10% OCT CSF thickness) since either of the last two injections

For eyes in the bevacizumab + deferred aflibercept group, the failure criteria cannot be applied prior to the eye switching to aflibercept and receiving 3 monthly injections of aflibercept.

### 4.3.4 Laser for DME

Treatment with focal/grid laser will not be permitted in the study eye(s) during the study unless failure criteria are met. If the failure criteria listed in 4.3.3 is met, treatment (including laser) is up to investigator discretion.

# 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 Use of Intravitreous Anti-VEGF for Conditions Other than DME in the Study Eye

Treatment for conditions other than DME is at investigator discretion. If a participant develops a diabetic eye disease, e.g. proliferative diabetic retinopathy in the study eye, for which the investigator intends to administer anti-VEGF treatment, it is recommended that the eye is treated with the same anti-VEGF drug being given for DME.

## 5.3 Treatment in Non-study Eye

Treatment of PDR or DME in the non-study 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 annual study visits will be performed. Study participants who have an adverse event 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 DRCR.net 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 will be maintained in a secure database and will be maintained separately from the study data.

Phone contact from the Coordinating Center may be made with each study participant in the first month after enrollment, and approximately every six months thereafter. Additional phone contacts or mailings from the Coordinating Center will be made to facilitate the scheduling of the study participant for follow-up visits. A study 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 study participants.

### 5.8 Study Participant Reimbursement

The study will be providing the study participant with a $25 merchandise or money card per completed non-annual study visit and $100 in merchandise or money cards per completed annual visit. 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 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/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, protocol, or informed consent form.

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 Potential Adverse Effects of Study Drugs

#### 6.5.1.1 Aflibercept

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

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

The DA VINCI study, a phase II study evaluating aflibercept for treatment of DME, reported common adverse events that were consistent with those previously seen with intravitreous injections. Over one year of follow-up, two cases of endophthalmitis and one case of uveitis occurred (all in aflibercept treatment groups). Seven deaths (4.0%) occurred in the groups randomized to aflibercept treatment as compared with 1 (2.3%) in the group treated with laser. Myocardial infarction or cerebrovascular accident occurred in 6 (3.4%) participants treated with aflibercept as compared with 1 (2.3%) participant treated with laser alone.[15] Percentages of study participants that experienced events meeting APTC criteria were 5.1% (N = 9) in the combined aflibercept groups and 4.5% (N = 2) in the laser group.[16]

The DRCR.net Protocol T study assessed ocular and systemic adverse events in eyes with center-involved DME treated with aflibercept over 1 year.[17] In the aflibercept-treated study eyes, there were no cases of endophthalmitis and 2 cases of ocular inflammation. Non-study eyes treated with aflibercept had 1 case of endophthalmitis and 3 cases of ocular inflammation. Systemic adverse events were infrequent with only 6 APTC events (4 nonfatal myocardial infarctions, 2 deaths from a potential vascular cause or unknown cause, 6% of participants) over the 1 year period in the aflibercept group.

Additional safety data were published from phase III studies VISTA and VIVID, which included 872 eyes with DME with central involvement that received either intravitreous aflibercept every 4 weeks, intravitreous 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.[18] 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).[19]

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

#### 6.5.1.2 Bevacizumab

In a meta-analysis performed by Genentech, Inc on all clinical trial results using intravenously administered bevacizumab (usually dose 5 mg/kg every 14 days), it was found that study participants were at an increased risk for certain adverse events, some of which were potentially fatal. These included wound healing complications, bowel perforation, hemorrhage, stroke, myocardial infarction, hypertension, congestive heart failure, and proteinuria. Warnings and

precautions included in the bevacizumab package insert for intravenously administered drug fall under the categories of gastrointestinal perforations, surgery and wound healing complications, hemorrhage, non-gastrointestinal fistula formation and fistulae, arterial thromboembolic events, venous thromboembolic events, hypertension, posterior reversible encephalopathy syndrome, proteinuria, infusion reactions, embryo-fetal toxicity and ovarian failure.[20]

In contrast, available data suggest that intravitreally-administered bevacizumab in substantially smaller doses (1.25 or 2.5 mg) appears to have a good safety profile with regard to ocular and systemic adverse events. No increased rates of thromboembolic events or death in bevacizumab versus control groups have been reported in smaller, prospective randomized studies including the DRCR.net Protocol H or the BOLT study.[21] Retrospective, observational data from larger patient groups also does not appear to indicate an increased risk of ocular or systemic events with intravitreal bevacizumab treatment. In 2006, an internet-based survey of 70 international sites from 12 countries was reported that described outcomes after 7,113 injections given to 5,228 patients. Rates were 0.21% or less for each category of doctor-reported adverse events, including blood pressure elevation, transient ischemic attack, cerebrovascular accident, death, endophthalmitis, retinal detachment, uveitis, or acute vision loss.[22] The PACORES group reported 12 month safety of intravitreal injections of 1.25 and 2.5 mg doses of bevacizumab given for a variety of conditions in a large group of study participants including 548 patients with diabetes.[23] A total of 1,174 patients were followed for at least 1 year. Systemic adverse events were reported in 1.5% (N = 18), including elevated blood pressure in 0.6% (7), cerebrovascular accidents in 0.5% (6), myocardial infarctions in 0.4% (5), iliac artery aneurysms in 0.2% (2), toe amputations in 0.2% (2), and deaths in 0.4% (5) of patients. The overall mortality rate of diabetic patients in this study was low at 0.55% (3/548). Ocular complication were reported as bacterial endophthalmitis in 0.2% (7), traction retinal detachments in 0.2% (7), uveitis in 0.1% (4), and a single case each of rhegmatogenous retinal detachment and vitreous hemorrhage. Finally, when bevacizumab is used to treat DME it does not appear to have a worse safety profile than other anti-VEGF agents. In the DRCR.net Protocol T randomized trial of 660 participants, Anti-Platelet Trialists' Collaboration (APTC) events occurred in 5% with aflibercept, 8% with bevacizumab, and 13 % with ranibizumab (global P = 0.047; aflibercept vs. bevacizumab, P = 0.34; aflibercept vs. ranibizumab, P = 0.047; ranibizumab vs. bevacizumab, P = 0.20).[13]

Recently reported results from the CATT Research Group also suggest that intravitreal bevacizumab is well tolerated. At one year, four of 286 participants (1.4%) in the monthly bevacizumab group had died and 11 of 300 participants (3.7%) in the bevacizumab given as needed group had died. Arteriothrombolic events occurred at a rate of 2.1% and 2.7% in the monthly bevacizumab and as needed bevacizumab groups, respectively. Venous thrombotic events occurred at rates of 1.4% and 0.3% in the monthly bevacizumab and as needed bevacizumab groups, respectively. Endophthalmitis occurred after 0.07% of injections in patients treated with bevacizumab. Although a higher rate of serious systemic adverse events was present in the bevacizumab group as compared with the ranibizumab group, the excess events in the bevacizumab group were primarily hospitalizations due to events not previously attributed to anti-VEGF treatment.[24] Differences in rates were largest for hospitalizations for infections (e.g., pneumonia and urinary tract infections) and gastrointestinal disorders (e.g., hemorrhage and nausea and vomiting). Two year follow-up safety data from the CATT study did not reveal significant differences in rates of arterial thromboembolic events or death between bevacizumab

and ranibizumab treated participants. Overall rates of serious adverse events, however, were higher among bevacizumab-treated patients (39.9%) than ranibizumab-treated patients (31.7%), with the greatest imbalance in gastrointestinal disorders not previously linked to anti-VEGF therapy.[25] In contrast, at 1 year in the IVAN study, fewer arteriothrombotic events or heart failure cases were seen in the bevacizumab treated group and there was no difference in the percentage of patients experiencing serious adverse events between the bevacizumab and ranibizumab treatment groupS.[26]

As noted in the introduction, bevacizumab has been given intravitreally to several thousand patients with age-related macular degeneration or diabetic macular edema in doses generally of 1.25 or 2.5 mg per injection (a fraction of the systemic dose). There have not been consistent reports suggestive of adverse systemic effects of the drug. This likely rules out serious systemic events being common but does not rule out the possibility of such events occurring rarely. Patients with diabetes are at increased risk for myocardial infarction, stroke, and renal disease. Thus, if a study participant develops a cardiovascular or renal problems, it may be due to the vascular effects of diabetes and other systemic factors and not related to bevacizumab. It is likely that only in a large study comparing adverse event rates between a bevacizumab-treated group and a control group will it be possible to determine if there is an excess of systemic adverse events with bevacizumab. At this time, we believe the chances of a serious systemic effect of bevacizumab are very small. However, we cannot rule out this possibility and there is evidence that systemic concentrations of VEGF may be reduced to an even greater extent with intravitreal bevacizumab as compared with ranibizumab treatment.[26] In view of the large number of eyes treated with bevacizumab injections, it also seems unlikely that the drug has a deleterious effect on the retina or other parts of the eye.

### 6.5.2 Potential Adverse Effects of Intravitreous 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 intravitreous 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 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 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.

For fluorescein angiography, both the skin and urine are expected to turn yellow/orange for up to 24 hours after the injection of fluorescein dye. There is a small risk of discomfort or phlebitis at the site of the injection. Patients occasionally experience lightheadness or nausea after dye injection which are usually transient and resolve after a few minutes without further intervention. An allergic reaction to the dye used to do the fluorescein angiography imaging is rare. A rash or pruritus (itching) can develop, but true anaphylactic reactions are very rare.

# 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 any tabulation or analysis of study data.

## 7.1 Primary Outcome

The sample size has been computed for the primary outcome, mean change in visual acuity over two years, measured using area under the curve (AUC).

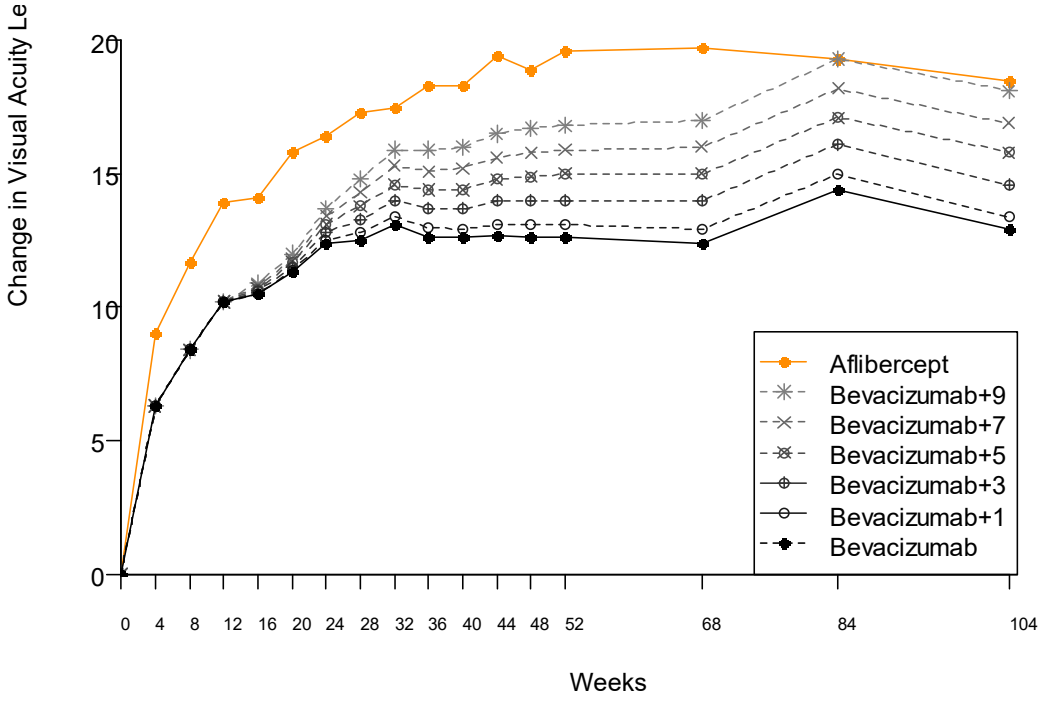
## 7.2 Sample Size

### 7.2.1 Outcome Projections

Data from DRCR.net Protocol T was used to estimate visual acuity outcomes in the two groups. Based on the switch criteria, it is estimated that approximately 58% of the bevacizumab group will receive aflibercept during the 2 years of the trial. It is anticipated that approximately half of these eyes will switch during the first 24 weeks of the trial, with the other half of the eyes that switch distributed across the remaining 18 months of the study.

Projected group means and required sample sizes were estimated for various scenarios after switching. Figure 1 presents estimates of change in visual acuity over 2 years (AUC) assuming that switching to aflibercept increases visual acuity at each visit in the bevacizumab group from 1 to 9 letters over what was observed in Protocol T.

**Figure 1.** Change in visual acuity with aflibercept, bevacizumab, or bevacizumab assuming that after switch criteria are met the eye gains 1, 3, 5, 7, or 9 letters more than what was observed with bevacizumab alone in Protocol T.



### 7.2.2 Sample Size Estimates

Table 1 below shows sample size estimates under varying assumptions for the effect of the switch to aflibercept in bevacizumab eyes (for the primary outcome of change in visual acuity AUC over 2 years). These calculations assume a Type I error rate of 4.9% (0.1% allocated for DSMC review), 90% power, and a two-sided test of superiority with a null hypothesis of no difference between groups.

**Table 1:** Sample size calculations.

| | **Protocol T (Switch + 0 letters)** | **Switch + 1 letter** | **Switch + 3 letters** | **Switch + 5 letters** | **Switch + 7 letters** | **Switch + 9 letters** |
|---|---|---|---|---|---|---|
| **Mean Change in Visual Acuity AUC** | | | | | | |
| Aflibercept | 17.4 | 17.4 | 17.4 | 17.4 | 17.4 | 17.4 |
| Bevacizumab + Deferred Aflibercept | 12.1 | 12.5 | 13.2 | 13.9 | 14.7 | 15.4 |
| Difference | 5.3 | 4.9 | 4.2 | 3.5 | 2.7 | 2.0 |
| Adjusted Standard Deviation* | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 |
| Total N | 116 | 136 | 184 | 264 | 442 | 802 |

*Adjusted for a correlation of 0.5 with baseline visual acuity. Standard deviation based on the Protocol T aflibercept group, which had a larger standard deviation than the bevacizumab group, making these estimates conservative.

The final sample size was calculated with the following assumptions:

- Mean change in visual acuity AUC in the aflibercept group = 17.4 letters
- Mean change in visual acuity AUC in the bevacizumab + deferred aflibercept group = 13.9 (assuming eyes that switch to aflibercept gain 5 letters more than they would have if the eye had remained on bevacizumab)
- Treatment group difference = 3.5 letters; Adjusted standard deviation = 8.7 letters
- Type I error rate = 4.9%; Power = 90%
- 15% increase for expected lost to follow-up

Based on the above assumptions, the total sample size is **312 participants (156 per treatment group)**.

## 7.3 Primary Analysis Plan

### 7.3.1 Principles for Analysis

The primary analysis consists of a treatment group comparison of mean change in visual acuity AUC over 2 years adjusted for baseline visual acuity. A linear mixed model with a random intercept term for participant will be used to control for correlations arising from participants contributing two study eyes to the analysis. AUC will be calculated for each participant by the trapezoidal rule using the following formula:

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

Where $V_i$ is the change in visual acuity measured at the $i^{th}$ visit, $d_i$ is the number of days between randomization and the $i^{th}$ visit, and $n$ is the number of outcome visits included in the analysis. 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 change in visual acuity over the time period between baseline and the $n^{th}$ visit.

All 4-week visits through 52 weeks as well as the 104 week visit will be included in the calculation of AUC as these are common to both treatment groups. Since visits can occur every 4 to 16 weeks in year 2, depending upon disease progression, analysis windows will be defined around 68 and 84 weeks for the purposes of calculating AUC. Thus, the visits to be included for calculation of the primary outcome are 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 68, 84, and 104 weeks.

The primary analysis is an "intent to treat analysis" that will include all randomized eyes according to treatment group assignment at randomization. Multiple imputation will be used to handle missing data.

### 7.3.2 Sensitivity Analyses

A sensitivity analysis using only observed data from eyes that complete the 104-week visit also will 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.

A per-protocol analysis will be conducted to estimate the treatment effect for each group among those not receiving any alternative treatment for DME (e.g., intravitreal corticosteroids). This analysis will include observed data from all randomized up to the time of alternative treatment for DME. Data collected after the alternative treatment will be set to missing prior to imputation. Imputation will otherwise be similar to the primary analysis.

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 using only observed data from eyes that complete the 104-week visit by including factors potentially associated with the outcome for which there is an imbalance between groups.

### 7.3.3 Subgroup Analyses

Pre-planned subgroup analyses, using observed data from eyes that complete the 104-week visit will be described in the Statistical Analysis Plan and will include analyses by prior treatment for DME, OCT CSF thickness, and baseline visual acuity. 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.

### 7.3.4 Interim Analysis Plan

There will be no formal interim analysis for efficacy or futility.

## 7.4 Secondary Outcomes for Treatment Group Comparison

The treatment groups will be compared on the following secondary outcomes of interest at the 52 and 104-week visits:

- Mean change in visual acuity from baseline (also compared at the 24-week visit)
- Percentages of eyes with a gain (increase) or loss (decrease) of at least 10 or at least 15 letters of visual acuity from baseline
- Percentages of eyes with visual acuity 20/20 or greater, 20/40 or greater, and 20/200 or worse
- Mean change in OCT central subfield thickness from baseline (also compared at the 24-week visit)
- Percentage of eyes with OCT central subfield thickness below the gender-specific spectral domain OCT equivalent of 250 µm on Zeiss Stratus OCT
- Mean change in OCT retinal volume
- Percentages of eyes with worsening or improvement of diabetic retinopathy on fundus photographs
- Percentage of eyes receiving panretinal photocoagulation, vitrectomy, or occurrence of vitreous hemorrhage, traction retinal detachment, neovascularization of the iris, or neovascular glaucoma from proliferative diabetic retinopathy
- Number of visits through 2 years
- Number of injections
- Percentage of eyes that met switch criteria by the 12, 24, 52, or 104-week visits (bevacizumab + deferred aflibercept group only)

Binary outcomes will be analyzed using binomial regression with generalized estimation equations (GEE) to control for correlations arising from participants contributing two study eyes to the analysis. If binomial regression fails to converge in one or more outcomes, then logistic regression with a random intercept for participant, conditional standardization, and the delta method (to estimate the risk difference)[27] may be used instead for all binary outcomes. Analyses will be adjusted for baseline measures where appropriate. All model assumptions, including linearity, normality of residuals, and homoscedasticity, will be verified. If model assumptions are not satisfied, then a transformation or a nonparametric analysis will be considered. Methods for handling missing secondary outcome data will be specified in the Statistical Analysis Plan.

## 7.5 Economic Analysis

The purpose of the economic analysis is to compare the treatment groups with respect to cost.

An incremental cost effectiveness ratio (ICER) will be calculated. Data from the clinical trial on number of clinic visits completed, number of procedures performed (e.g., OCT, fundus photographs), and number of aflibercept and bevacizumab treatments will be used to estimate an average cost per patient for each treatment arm, using the Medicare Fee Schedule to estimate medical costs.

For outcomes measured at the participant level, bilateral participants are non-informative with respect to the treatment comparison and will not be included in the analyses.

### 7.6 Safety Analysis Plan

Ocular adverse events will be tabulated separately for the two treatment groups. The frequency of each event occurring at least once per eye will be calculated. The percentage of eyes experiencing each outcome will be compared between treatment groups using Barnard's unconditional exact test and considering the number of eyes in each treatment group as fixed. It is noted that this method does not adjust for the potential correlations arising from participants with two study eyes; however, given the low expected frequency of adverse events, and small proportion of bilateral subjects, the impact should be minimal.

The following ocular adverse events are of primary interest:

- Endophthalmitis
- Retinal detachment
- Traumatic cataract
- Vitreous hemorrhage
- Ocular inflammation
- Intraocular pressure elevation
- Neovascular glaucoma
- Iris neovascularization

Systemic adverse events will be reported in three groups: 1) unilateral participants randomized to bevacizumab + deferred aflibercept, 2) unilateral participants randomized to aflibercept, and 3) bilateral participants randomized to bevacizumab + deferred aflibercept in one eye and aflibercept in the other eye. The frequency of each event occurring at least once per participant will be calculated. The percentage of participants experiencing each outcome will compared with Fisher's exact test. If the overall test has $P \leq 0.05$, then pairwise comparisons between groups also will be conducted using Fisher's exact test without further adjustment for multiple comparisons.

The following systemic adverse events are of primary interest:

- 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 cause (does not need to be ischemic in origin), or unknown cause
    - Notes: Transient ischemic attacks, angina, and possible myocardial infarction or stroke are not counted. Nonfatal myocardial infarction or stroke require that the participant be alive at the end of the study. If not, only the death is counted.

- Secondary systemic adverse events of interest:
  - For each MedDRA system organ class, percentage of participants with at least one event

A tabulation of all study eye ocular, non-study eye ocular, and systemic adverse events will be tabulated according to treatment group as described above.

## 7.7 Additional Tabulations and Analyses

The following will be tabulated according to treatment group:

1) Baseline demographic and clinical characteristics
2) Visit completion rate
3) Treatment adherence

## 7.8 Multiple Testing

The primary analysis will be conducted at alpha of 0.05. If the primary analysis demonstrates a significant treatment group difference, then mean change in visual acuity from baseline at 104 weeks and mean change in OCT central subfield thickness from baseline at 104 weeks will be tested as secondary outcomes. The Holm method will be used to provide strong control of alpha at 0.05.[28] If the primary analysis fails to show a significant difference, then outcomes will be described with summary statistics, model-based point estimates, and between-group 95% confidence intervals without P values. This approach controls the family-wise error rate at 5%.

There will be no formal adjustment for multiplicity in sensitivity, subgroup, or safety analyses. For exploratory subgroup analyses, the number of significant results expected by chance given the number of comparisons will be noted.

# CHAPTER 8
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