

Diabetic Retinopathy Clinical Research Network

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

Version 1.0

October 6, 2011

Contact Information

Coordinating Center

Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647
Phone: 813-975-8690
Fax: 800-816-7601

Director: Adam Glassman, M.S.
Email: aglassman@jaeb.org

Network Chair

Neil M. Bressler, MD
Wilmer Eye Institute – Johns Hopkins
600 North Wolfe Street
Baltimore, MD 21287-9226
Phone: (410) 955-8342
Fax: (410) 955-0845
Email: nbressler@jhmi.edu

1 **Table of Contents**

2 **Chapter 1. Background Information and Study Synopsis..... 1-1**

3 1.1 Background and Rationale..... 1-1

4 1.1.1 Public Health Impact of Diabetic Retinopathy 1-1

5 1.1.2 Proliferative Diabetic Retinopathy: Impact on Vision Loss, Treatment, and

6 Complications from Treatment..... 1-1

7 1.1.3 Rationale for Anti-VEGF Therapy for PDR..... 1-2

8 1.2 Study Objectives and Hypothesis 1-4

9 1.3 Study Design and Synopsis of Protocol..... 1-5

10 1.4 General Considerations..... 1-7

11 **Chapter 2. Study Participant Eligibility and Enrollment 2-1**

12 2.1 Identifying Eligible Study Participants and Obtaining Informed Consent 2-1

13 2.2 Study Participant Eligibility Criteria 2-1

14 2.2.1 Individual-level Criteria..... 2-1

15 2.2.2 Study Eye Criteria..... 2-2

16 2.3 Screening Evaluation and Baseline Testing..... 2-4

17 2.3.1 Historical Information..... 2-4

18 2.3.2 Baseline Testing Procedures 2-4

19 2.4 Enrollment/Randomization of Eligible Study participants 2-5

20 **Chapter 3. Follow-up Visits and Testing 3-1**

21 3.1 Visit Schedule 3-1

22 3.1.1 Assessment Visits 3-1

23 3.1.2 Treatment Visits for PDR 3-1

24 3.1.2 Treatment Visits for DME 3-2

25 3.2 Testing Procedures..... 3-2

26 **Chapter 4. Treatment Regimen 4-1**

27 4.1 Introduction..... 4-1

28 4.2 Intravitreal Injection Treatment for PDR During Follow Up in the Ranibizumab with

29 Deferred PRP Group 4-1

30 4.2.1 Intravitreal Injection at 4-week, 8-week and 12-week Follow-up Visits..... 4-1

31 4.2.2 Intravitreal Injection at and after the 16-week Follow-up Visit 4-1

32 4.2.3 Next Retreatment Evaluation..... 4-3

33 4.3 Panretinal Photocoagulation Treatment During Follow-up..... 4-3

34 4.3.1 Deferral of Additional Scatter Photocoagulation for Decreased Visual Acuity from

35 Exacerbation of Macular Edema..... 4-4

36 4.3.2 Additional Scatter Photocoagulation for Proliferative Diabetic Retinopathy..... 4-4

37 4.4 Treatment for Diabetic Macular Edema 4-4

38 4.4.1 Intravitreal Injection Retreatment Guidelines for DME 4-5

39 4.4.2 Focal/Grid Photocoagulation Treatment for DME during Follow-Up 4-6

40 4.4.3 Next Retreatment Evaluation..... 4-7

41 4.5 Ranibizumab (Lucentis™)..... 4-7

42 4.5.1 Intravitreal Injection Technique..... 4-8

43 4.5.2 Deferral of Injections Due to Pregnancy 4-8

44 4.5.3 Delay in Giving Injections..... 4-8

45 4.6 Panretinal Photocoagulation Technique 4-8

46	4.7 Focal/Grid Photocoagulation Technique	4-9
47	Chapter 5. Miscellaneous Considerations in Follow-up.....	5-1
48	5.1 Endophthalmitis	5-1
49	5.2 Surgery for Vitreous Hemorrhage, Traction Detachment, and Other Complications of	
50	Diabetic Retinopathy	5-1
51	5.3 Treatment of Macular Edema in Nonstudy Eye	5-1
52	5.4 Diabetes Management.....	5-1
53	5.5 Study Participant Withdrawal and Losses to Follow-up.....	5-1
54	5.6 Discontinuation of Study	5-1
55	5.7 Contact Information Provided to the Coordinating Center.....	5-1
56	5.8 Study Participant Reimbursement.....	5-2
57	Chapter 6. Adverse Events.....	6-1
58	6.1 Definition	6-1
59	6.2 Recording of Adverse Events	6-1
60	6.3 Reporting Serious or Unexpected Adverse Events.....	6-2
61	6.4 Data and Safety Monitoring Committee Review of Adverse Events	6-2
62	6.5 Risks.....	6-3
63	6.5.1 Ranibizumab	6-3
64	6.5.2 Potential Adverse Effects of Intravitreal Injection	6-3
65	6.5.3 Risks of Focal/Grid Photocoagulation Treatment.....	6-4
66	6.5.4 Risks of Panretinal Photocoagulation Treatment.....	6-4
67	6.5.5 Risks of Eye Examination and Tests	6-4
68	Chapter 7. Statistical Methods.....	7-1
69	7.1 Sample Size.....	7-1
70	7.1.1 Sample Size Assumptions.....	7-1
71	7.1.2 Non-Inferiority Margin	7-1
72	7.1.3 Sample Size Estimations.....	7-2
73	7.2 Efficacy Analysis Plan.....	7-2
74	7.2.1 Principles for Analysis.....	7-2
75	7.2.2 Secondary Outcomes for Treatment Group Comparison.....	7-4
76	7.2.3 Safety Analysis Plan	7-7
77	7.2.4 Additional Tabulations and Analyses	7-8
78	7.2.5 Interim Analysis Plan.....	7-8
79	Chapter 8. References.....	8-1
80		

81
82 **CHAPTER 1. BACKGROUND INFORMATION AND STUDY SYNOPSIS**
83

84 **1.1 Background and Rationale**

85 **1.1.1 Public Health Impact of Diabetic Retinopathy**

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

96
97 Advancing diabetic retinopathy is characterized by increasing retinal ischemia. The anatomic
98 sequel of this pathophysiologic change, retinal neovascularization or PDR, is a major cause of
99 preventable and potentially irreversible vision loss in patients with diabetes. Data from the
100 Diabetic Retinopathy Study suggest that given long enough duration of diabetes, approximately
101 60% of patients with diabetes melitus will develop PDR. Without intervention, nearly half of
102 these eyes with PDR will experience profound visual loss (Snellen visual acuity worse than
103 5/200) from associated complications including vitreous hemorrhage and/or tractional retinal
104 detachment.⁴

105
106 **1.1.2 Proliferative Diabetic Retinopathy: Impact on Vision Loss, Treatment, and**
107 **Complications from Treatment**

108 The initial manifestation of PDR is retinal neovascularization at the disc or elsewhere. Vitreous
109 hemorrhage and tractional retinal detachment from PDR are important causes of severe visual
110 loss and new onset blindness in developed countries worldwide. According to Aiello (2005),
111 despite advances in the treatment of both diabetes and diabetic retinopathy, in the United States
112 alone there are approximately 700,000 persons with PDR, with 63,000 new cases of proliferative
113 retinopathy annually. Furthermore, the Centers for Disease Control and Prevention reported in
114 2007 that there are 12,000-24,000 new cases of diabetic retinopathy-induced blindness each
115 year.^{2,5}

116
117 PDR is currently treated with scatter or panretinal photocoagulation (PRP) which destroys areas
118 of retina but preserves central vision. Multicenter clinical trials have demonstrated the
119 effectiveness of PRP in preserving vision and reducing the risk of vision loss.^{6,7} The Early
120 Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that PRP applied when an eye
121 approaches or just reaches high risk PDR reduces the risk of severe vision loss to less than 4%.⁸
122 Subsequent analyses of the ETDRS data revealed that early PRP was also effective in preventing
123 severe visual loss specifically in patients with type 2 diabetes who had severe non-proliferative
124 diabetic retinopathy (NPDR) or early PDR.⁹

125
126 In PRP, typically 1200 to 1800 laser burns (approximately 500 μ m in size on the retina) are
127 applied to the peripheral retinal tissue, focally destroying outer photoreceptors and retinal

128 pigment epithelium. Large vessels are avoided, as are areas of pre-retinal hemorrhage. The
129 treatment is thought to exert its effect by increasing oxygen delivery to the inner retina and
130 decreasing viable hypoxic cells which are producing growth factors such as VEGF. The total
131 treatment is usually applied over one to four sessions, spaced one to two weeks apart. Follow-up
132 evaluation usually occurs at one month, and then three to four months after completion of
133 treatment. Response to PRP varies, while it is most desirable to see a regression of new vessels,
134 stabilization of neovascularization with no further growth may also result.
135

136 Occasionally, macular edema may develop or pre-existing DME may worsen following PRP.^{10, 11}
137 The ETDRS, which was performed prior to OCT availability, found that among eyes with no
138 central retinal thickening at baseline in graded fundus photographs, retinal thickening was
139 present at 4 months in 16% of eyes that underwent full PRP compared with 12% in eyes for
140 which scatter photocoagulation was not performed.¹² Furthermore, in patients with center-
141 involved DME requiring PRP who also receive focal/grid laser, exacerbation of macular edema
142 associated with visual acuity loss has also been documented.^{11, 13} Unpublished data from the
143 ETDRS shows that 14% of eyes with some PDR (level 61 or worse) and macular edema with
144 center involvement at initiation of PRP lose at least 10 letters of vision from baseline to 4
145 months, while 14% also lose at least 15 letters at 4 months (unpublished data from the ETDRS
146 analyzed by Coordinating Center for the DRCR Network).
147

148 Although remarkably effective at reducing visual loss if applied in a timely and appropriate
149 manner, PRP treatment destroys viable retinal tissue and is associated with well-documented
150 potential side effects in addition to exacerbation of macular edema that may lead to transient or
151 permanent loss of visual function, including peripheral visual field defects, night vision loss, loss
152 of contrast sensitivity, potential complications from misdirected or excessive burns, and
153 progression of visual loss in nearly 5% of individuals despite appropriate treatment.¹⁴ Because
154 of these side effects, there is interest and rationale, from a public health point of view, for
155 exploring therapeutic alternatives that might delay or obviate the need for this inherently
156 destructive procedure, since PRP-associated vision loss may lead to lost work time, lost wages,
157 decreased ability to care for diabetes, or decreased ability to drive safely.
158

159 **1.1.3 Rationale for Anti-VEGF Therapy for PDR**

160 Multiple studies have implicated VEGF as a major causative factor in human eye diseases
161 characterized by neovascularization, including PDR.¹⁵⁻²⁵ Thus, inhibition of VEGF would be
162 expected to reduce PDR.
163

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

176 200 fold less than the standard clinically used dose of 1.25 mg. Another small prospective,
177 open-label exploratory study randomized 20 subjects with active PDR to treatment with
178 intravitreal pegaptanib versus PRP. By week 12, all pegaptanib-treated eyes demonstrated
179 complete regression of neovascularization, which was maintained through the final study visit at
180 week 36.³²

181
182 As indicated above, the current standard treatment for PDR is PRP, but this treatment is
183 inherently destructive and has several potential adverse effects on aspects of visual function,
184 including constriction of peripheral visual fields and decreases in night vision, contrast
185 sensitivity and color perception. Thus, therapeutic alternatives that might delay or obviate the
186 need for PRP are desirable. It is possible that anti-VEGF treatment could prevent laser-
187 associated vision loss by precluding the need for PRP as long as the eye continued to receive it.
188 Even if anti-VEGF treatment was discontinued and there was an eventual need for PRP due to
189 recurrent, active PDR, it is possible that initial treatment with anti-VEGF therapy might improve
190 visual outcomes substantially by delaying or preventing the need for PRP.

191

192 **1.1.3.1 Role of Anti-VEGF Treatment in Eyes with PDR + DME**

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

213

214 The Protocol I results provided definitive confirmation of the promising role of anti-VEGF
215 therapy suggested by phase 2 trials (DRCR.net Protocol H, READ2, RESOLVE)^{33, 34} and
216 recently were confirmed in reports (not yet published) from similarly designed phase III trials
217 (RESTORE, RISE, RIDE),^{35, 37-39} that evaluated anti-VEGF therapy for maintaining or
218 improving vision in substantial proportions of patients with central DME and at least some visual
219 acuity impairment. Given the widespread influence of previous DRCR.net studies on United
220 States practice patterns for treatment of DME (e.g., the marked drop in nationwide use of
221 intravitreal steroid for DME after the publication of the Protocol B primary paper⁴⁰), it
222 is expected that the results from Protocol I will similarly influence retina physicians with regard to
223 treatment of center-involved DME, with a corresponding rise in the use of anti-VEGF therapy
224 for DME. Given the high likelihood that beginning this year, eyes with PDR and DME will

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

229
230 **1.1.3.2 Ranibizumab**
231 Ranibizumab, the anti-VEGF drug to be used in this trial, is a humanized monoclonal antibody
232 fragment which binds to and inhibits VEGF in the extracellular space. It is designed to block all
233 isoforms of VEGF-A. It was approved by the FDA as treatment for neovascular age-related
234 macular degeneration in 2006 and approved for treatment of macular edema from branch or
235 central retinal vein occlusions in 2010. Intravitreal ranibizumab in doses up to 2 mg appear to be
236 well tolerated.⁴¹ Although studies of ranibizumab as treatment for PDR have been limited to
237 date likely due to the high cost of the drug, it is known to be highly effective in the treatment of
238 ocular neovascularization associated with age-related macular degeneration.⁴² Furthermore,
239 preliminary data from Protocol I reveal that eyes assigned to the ranibizumab treated groups
240 were less likely to have a vitreous hemorrhage or receive PRP than the sham+prompt laser group
241 (3% versus 7%) during the first year of follow up, and less likely to progress from severe NPDR
242 to PDR (8% versus 42%), even though ranibizumab was not given monthly to all study
243 participants following the 12-week visit, suggesting a beneficial effect of ranibizumab treatment
244 on diabetic retinal neovascularization which might not require monthly treatments indefinitely to
245 achieve this beneficial effect.³⁶

246
247 **1.1.4. Summary of Rationale**
248 Current standard treatment for PDR is PRP, but this treatment is inherently destructive and has
249 several potential adverse effects on aspects of visual function, including constriction of
250 peripheral visual fields and decreases in night vision, contrast sensitivity and color perception.
251 Thus, therapeutic alternatives that might delay or obviate the need for PRP are desirable. It has
252 been demonstrated that retinal neovascularization from PDR is highly responsive to anti-VEGF
253 therapy, but it is unclear how long regression of retinal neovascularization is sustained after anti-
254 VEGF therapy is halted. It is possible that intravitreal ranibizumab treatment could prevent
255 laser-associated vision loss by precluding the need for PRP as long as the eye continued to
256 receive ranibizumab. Even if ranibizumab treatment was discontinued, it is possible that initial
257 treatment with anti-VEGF therapy might improve visual outcomes substantially by delaying or
258 preventing the need for PRP, and the infrequent frequency of administration of ranibizumab for
259 DME (median 2 to 3 times in the second year of treatment) after the DME initially has resolved
260 on anti-VEGF therapy suggests that monthly ranibizumab might not be needed to achieve control
261 of PDR.

262 **1.2 Study Objectives and Hypothesis**
263 The primary objective of the protocol is to determine if visual acuity outcomes at 2 years in eyes
264 with PDR that receive anti-VEGF therapy with deferred PRP are non-inferior to those in eyes
265 that receive standard prompt PRP therapy.

266
267 Secondary objectives include:

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

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

275 **1.3 Study Design and Synopsis of Protocol**

276 **A. Study Design**

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

278

279 **B. Major Eligibility Criteria**

- 280 • Age ≥ 18 years
- 281 • Type 1 or type 2 diabetes
- 282 • Study eye with
 - 283 ○ PDR for which PRP can be safely deferred for at least 4 weeks in the investigator's
 - 284 judgment.
 - 285 ○ No prior PRP (prior PRP is defined as ≥ 100 burns placed previously outside of the
 - 286 posterior pole)
 - 287 ○ Visual acuity letter score in the study eye ≥ 24 (approximate Snellen equivalent of
 - 288 20/320 or better)

289 **C. Treatment Groups**

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

291

- 292 • Prompt panretinal photocoagulation
- 293 • Intravitreal 0.5 mg ranibizumab with deferred panretinal photocoagulation

294

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

298

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

301

302 **D. Sample Size**

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

305

306 **E. Duration of Follow-up**

- 307 • Primary outcome: 2 years
- 308 • Total follow-up: 5 years

309

310 **F. Follow-up Schedule**

- 311 • Year 1: For eyes assigned to the ranibizumab with deferred PRP group, follow-up visits
312 occur every 4 weeks unless PRP is given (see section 3.1.2). For eyes assigned to the
313 prompt PRP group, follow-up visits occur every 16 weeks. Eyes may be seen more
314 frequently for DME treatment as needed.
- 315 • Years 2 and 3: Follow-up visits occur every 4 to 16 weeks depending on disease
316 progression and treatment administered (see section 3.1.2).
- 317 • During years 4 and 5, treatment and follow-up is performed as part of the study
318 participant's usual care; study visits occur only at 4 and 5 years.

319
 320
 321
 322
 323
 324
 325
 326
 327
 328
 329
 330
 331
 332
 333
 334
 335
 336
 337
 338
 339
 340
 341
 342
 343
 344
 345
 346
 347
 348
 349
 350
 351
 352

G. Main Efficacy Outcomes

1. Treatment group comparisons:

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

Secondary:

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

2. Assessment of treatment group receiving anti-VEGF with deferred PRP:

- Percent not requiring PRP in the deferred PRP group at 2 years

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

H. Main Safety Outcomes

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

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

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

I. Schedule of Assessment Visits and Examination Procedures

Visit Window	0	Treatment Visits Every 4-16w*	16w and 32w	52w	68w and 84w	104w	120w and 136w	156w	208w and 260w
		(+/- 1w)	(+/- 2w)	(+/- 2w)	(+/- 4w)	(+/- 4w)	(+/- 4w)	(+/- 4w)	(+/- 8w)
E-ETDRS best corrected visual acuity ^a	X	X	X	X	X	X	X	X	X
Binocular visual acuity ^b	X			X		X		X	X

Ancillary visual field testing ^c	X			X		X		X	X
Questionnaires ^d	X		X	X	X	X	X	X	X
OCT ^e	X	X		X		X		X	X
Eye Exam ^f	X	X	X	X	X	X	X	X	X
Fundus Photography ^g	X			X		X		X	X
Blood pressure	X								
HbA1c ^h	X								

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

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

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

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

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

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

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

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

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

373 1.4 General Considerations

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

377
378 The DRCR.net Procedures Manuals (visual acuity-refraction testing procedures manual,
379 photography procedures manual, OCT procedures manuals, and study-specific procedures
380 manual) provide details of the examination procedures and intravitreal injection procedure.

381
382 Data will be directly collected in electronic case report forms, which will be considered the
383 source data.

384
385 There is no restriction on the number of study participants to be enrolled by a site.
386

387
388
389

CHAPTER 2. STUDY PARTICIPANT ELIGIBILITY AND ENROLLMENT

390 **2.1 Identifying Eligible Study Participants and Obtaining Informed Consent**

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

397
398 Potential eligibility will be assessed as part of a routine-care examination. Prior to completing
399 any procedures or collecting any data that are not part of usual care, written informed consent
400 will be obtained. For patients who are considered potentially eligible for the study based on a
401 routine-care exam, the study protocol will be discussed with the potential study participant by a
402 study investigator and clinic coordinator. The potential study participant will be given the
403 Informed Consent Form to read. Potential study participants will be encouraged to discuss the
404 study with family members and their personal physician(s) before deciding whether to participate
405 in the study.

406
407 Consent may be given in two stages (if approved by the IRB). The initial stage will provide
408 consent to complete any of the screening procedures needed to assess eligibility that have not
409 already been performed as part of a usual-care exam. The second stage will be obtained prior to
410 randomization and will be for participation in the study. A single consent form will have two
411 signature/date lines for the study participant: one for a study participant to give consent for the
412 completion of the screening procedures and one for the study participant to document consent for
413 the randomized trial. Study participants will be provided with a copy of the signed Informed
414 Consent Form.

415
416 Once a study participant is randomized, that participant will be counted regardless of whether the
417 assigned treatment is received. Thus, the investigator must not proceed to randomize an
418 individual until he/she is convinced that the individual is eligible and will accept assignment to
419 any one of the 2 treatment groups.

420

421 **2.2 Study Participant Eligibility Criteria**

422 **2.2.1 Individual-level Criteria**

423 Inclusion

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

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

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

435 3. At least one eye meets the study eye criteria listed in section 2.2.2.

436 4. Able and willing to provide informed consent.

437 Exclusion

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

439 5. Significant renal disease, defined as a history of chronic renal failure requiring dialysis or
440 kidney transplant.

441 6. A condition that, in the opinion of the investigator, would preclude participation in the study
442 (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic
443 control).

444 • *Individuals in poor glycemic control who, within the last 4 months, initiated intensive*
445 *insulin treatment (a pump or multiple daily injections) or plan to do so in the next 4*
446 *months should not be enrolled.*

447 7. Participation in an investigational trial within 30 days of randomization that involved
448 treatment with any drug that has not received regulatory approval for the indication being
449 studied.

450 • *Note: study participants cannot receive another investigational drug while participating*
451 *in the study.*

452 8. Known allergy to any component of the study drug.

453 9. Blood pressure > 180/110 (systolic above 180 or diastolic above 110).

454 • *If blood pressure is brought below 180/110 by anti-hypertensive treatment, individual*
455 *can become eligible.*

456 10. Myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient
457 ischemic attack, or treatment for acute congestive heart failure within 4 months prior to
458 randomization.

459 11. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.

460 • *These drugs should not be used during the study.*

461 12. For women of child-bearing potential: pregnant or lactating or intending to become pregnant
462 within the next 3 years.

463 • *Women who are potential study participants should be questioned about the potential for*
464 *pregnancy. Investigator judgment is used to determine when a pregnancy test is needed.*

465 13. Individual is expecting to move out of the area of the clinical center to an area not covered by
466 another DRCR.net certified clinical center during the 3 years of the study.

467

468 **2.2.2 Study Eye Criteria**

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

471

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

475

476 The eligibility criteria for a study eye are as follows:

477

478 Inclusion

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

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

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

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

489

490 Exclusion

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

493

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

496 e) Tractional retinal detachment involving the macula.

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

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

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

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

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

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

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

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

- 519 k) History of corticosteroid treatment (intravitreal or peribulbar) at any time in the past 4
520 months.
- 521 • *If the investigator believes that there may still be a substantial effect 4 months after prior*
522 *treatment (e.g., dose of intravitreal triamcinolone higher than 4 mg), the eye should not*
523 *be included.*
- 524 l) History of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, any
525 intraocular surgery, etc.) within prior 4 months or anticipated within the next 6 months
526 following randomization.
- 527 m) History of YAG capsulotomy performed within 2 months prior to randomization.
- 528 n) Aphakia.
- 529 o) Uncontrolled glaucoma (in investigator’s judgment).
- 530 p) Exam evidence of severe external ocular infection, including conjunctivitis, chalazion, or
531 substantial blepharitis.

532

533 **2.3 Screening Evaluation and Baseline Testing**

534 **2.3.1 Historical Information**

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

539 **2.3.2 Baseline Testing Procedures**

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

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

557

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

- 563 3. Humphrey visual field testing using 30-2 and 60-4 test patterns; if site has the capability.
564 (*within 14 days prior to randomization*)
- 565 4. Questionnaires. (*only in participants with one study eye; within 14 days prior to*
566 *randomization*)
- 567 • NEI Visual Functioning Questionnaire-25 (*NEI-VFQ; measures the dimensions of*
568 *self-reported vision-targeted health status that are most important for individuals*
569 *who have chronic eye diseases*),
 - 570 • UAB Low Luminance Questionnaire (*UAB-LLQ; a 32-item questionnaire designed to*
571 *assess self-reported visual problems under low luminance and at night for use in*
572 *studies on age-related maculopathy*)
 - 573 • Time Trade-Off Questionnaire (*TTO; rating-scale technique used to calculate*
574 *quality-adjusted life years*); *not required for randomization.*
 - 575 • Workplace Productivity and Activity Impairment Questionnaire (*WPAI; a 6-item*
576 *questionnaire that collects data on employment and whether vision problems are*
577 *thought to affect productivity*); *not required for randomization.*
- 578 5. OCT in the study eye on DRCR.net-approved time domain or spectral domain OCT machine.
579 (*within 8 days prior to randomization*)
- 580 • *Investigator must verify accuracy of OCT scan by ensuring it is centered and of*
581 *adequate quality*
- 582 6. Ocular examination of each eye including slit lamp, measurement of intraocular pressure,
583 lens assessment, and dilated ophthalmoscopy on the study eye; examination of the angle is
584 required if neovascularization of the iris is present or increased intraocular pressure (IOP)
585 defined as ≥ 30 mm Hg (*on day of randomization*)
- 586 7. ETDRS protocol 7 standard-field or 4 wide-field digital stereoscopic fundus photography in
587 the study eye; if neovascularization is not captured on the standard photographs, additional
588 fields should be taken as necessary to confirm presence of PDR (*within 21 days prior to*
589 *randomization*)
- 590 8. Measurement of blood pressure
- 591 9. Laboratory testing- Hemoglobin A1c
- 592 • *HbA1c does not need to be repeated if available in the prior 3 months. If not available at*
593 *the time of randomization, the potential study participant may be enrolled but the test*
594 *must be obtained within 3 weeks after randomization.*

595 **2.4 Enrollment/Randomization of Eligible Study participants**

- 596 1. Prior to randomization, the study participant's understanding of the trial, willingness to
597 accept the assigned treatment group, and commitment to the follow-up schedule should be
598 reconfirmed.
- 599 2. The baseline treatment (injection and/or PRP according to treatment group assignment and
600 presence of DME) must be initiated on the day of randomization; therefore, a study
601 participant should not be randomized until this is possible. For study participants with two
602 study eyes that will be treated with ranibizumab at baseline, both eyes may be injected on the
603 same day or on separate days as long as the second eye is injected within one week of
604 randomization.

- 605 3. Randomization is completed on the DRCR.net website.
- 606 • Study participants with one study eye will be randomly assigned (stratified by site and
- 607 presence or absence of central involved DME) with equal probability to one of the
- 608 treatment groups:
- 609 ○ Group A: Prompt PRP
- 610 ○ Group B: 0.5 mg ranibizumab with deferred PRP
- 611
- 612 • For study participants with two study eyes (both eyes eligible at the time of
- 613 randomization),
- 614 ○ The study participant will be randomized with equal probability to receive either:
- 615 ■ Group A in the eye with greater OCT central subfield and Group B in the
- 616 eye with lower OCT central subfield
- 617 ■ Group B in the eye with greater OCT central subfield and Group A in the
- 618 eye with lower OCT central subfield
- 619 Note: if both eyes have the same OCT central subfield, the right eye will be considered
- 620 the eye with the greater OCT central subfield.

621

622 Presence of DME will be defined on OCT central subfield as ≥ 250 microns on Zeiss Stratus

623 OCT (or equivalent thickness on spectral domain OCT machine).

624

625
626
627

CHAPTER 3. FOLLOW-UP VISITS AND TESTING

628 3.1 Visit Schedule

629 3.1.1 Assessment Visits

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

632

633 Year 1

- 634 • Visits at 16, 32, 52 (± 2 weeks)

635

636 Years 2 and 3

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

638

639 Years 4 and 5

- 640 • Visits at 208 and 260 weeks (± 8 weeks)

641

642 3.1.2 Treatment Visits for PDR

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

646

647 Year 1

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

656

657 Years 2 and 3

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

665

666 Years 4 and 5

- 667 • Annual assessment visits only. Treatment and follow-up at investigator discretion (as
668 part of usual care)

669

670 **3.1.2 Treatment Visits for DME**

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

674 **3.2 Testing Procedures**

675 The following procedures will be performed at each protocol visit on the study eye only unless
676 otherwise specified. A grid in section 1.3 summarizes the testing performed at each visit. Visual
677 acuity testers and OCT technicians will be masked to treatment group at annual visits.
678

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

707
708 All of the testing procedures do not need to be performed on the same day, provided that they are
709 completed within the time window of a visit and prior to initiating any retreatment.
710

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

714
715
716

CHAPTER 4. TREATMENT REGIMEN

717 **4.1 Introduction**

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

- 719 • A: Prompt PRP
- 720 • B: 0.5mg ranibizumab with deferred PRP

721
722 For both treatment groups, study intravitreal ranibizumab must be given at baseline if OCT
723 central subfield thickness is ≥ 250 microns on Zeiss Stratus (or or equivalent thickness on spectral
724 domain OCT machine) and visual acuity is ≤ 78 (20/32 or worse). Study intravitreal ranibizumab
725 may be given for DME that develops during follow-up at the discretion of the investigator (non-
726 study anti-VEGF drugs or alternative treatments for DME should not be given).

727
728 Eyes assigned to ranibizumab with deferred PRP or with DME present at baseline will be given
729 the initial injection on the day of randomization. For study participants with two study eyes that
730 will be treated with ranibizumab, both eyes may be injected on the day of randomization or on
731 separate days. If the injections will occur on separate days, the second eye must be injected
732 within one week of the first injection given on the day of randomization.

733
734 Eyes assigned to the prompt PRP group will receive panretinal photocoagulation, which is
735 initiated on the day of randomization for eyes without DME or initiated within 0 to 14 days of
736 baseline injection if DME is present at baseline for which intravitreal ranibizumab is indicated (if
737 performed on the same day, PRP must be performed prior to injection).

738
739 The timing and criteria for retreatment for PDR and DME with ranibizumab and assessment for
740 PRP in the deferred PRP group are detailed in sections 4.2-4.4 below. Treatment procedures are
741 described in sections 4.5-4.7.

742 **4.2 Intravitreal Injection Treatment for PDR During Follow Up in the Ranibizumab with** 743 **Deferred PRP Group**

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

745 **4.2.1 Intravitreal Injection at 4-week, 8-week and 12-week Follow-up Visits**

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

750 **4.2.2 Intravitreal Injection at and after the 16-week Follow-up Visit**

751
752 Starting at the 16-week visit, study eyes randomized to receive ranibizumab with deferred PRP
753 will be evaluated for retreatment with intravitreal injection for PDR based on appearance of
754 neovascularization.

755
756
757 If an eye has experienced adverse effects from prior intravitreal injection treatment, retreatment
758 with intravitreal ranibizumab is at the discretion of the investigator. In addition, if any future
759 treatment with ranibizumab is contraindicated based on a previous adverse reaction, treatment

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

764
765 ** Note: examination of the angle is required if NV of the iris or increased IOP (see definition in*
766 *section 3.2) is present ; otherwise it is at investigator discretion; however, if the angle is*
767 *examined, then the results from this examination should be factored into the subsequent*
768 *treatment decision.*

769
770 • **Resolved**

771 ○ NV (of the retina, disc, AND iris/angle*) is absent and visualization of the entire
772 retina is adequate to completely assess for NV. Decision to re-inject is at
773 investigator discretion. In general, if NV is completely regressed the injection
774 should be deferred. PRP should not be given.
775

776 • **Improved**

777 NV (of the retina, disc OR iris/angle*) still persists, but there is evidence of
778 improvement (improvement defined as a decrease in the size of NV or diminished
779 density of NV) since the last visit and visualization of the entire retina is adequate
780 to completely assess for NV. An injection is given. PRP should not be given.
781

782 • **Stable**

783 ○ NV (of the retina, disc AND iris/angle*) is clinically unchanged since the last
784 visit and visualization of the entire retina is adequate to completely assess for NV.
785 Once the eye meets criteria for stability, at least 2 more injections must be given,
786 each one month apart (one at the visit at which stability criteria are met and the
787 second at the following study visit one month later if still stable). Further
788 reinjection is then at investigator discretion as long as the eye remains stable.
789 PRP should not be given.
790

791 • **Not fully treated**

792 ○ Failure/futility criteria not met and recurrent or worsening NV (of the retina, disc
793 OR iris) is present since the last visit in an eye that has had fewer than 4 injections
794 over the previous 4 months or there is vitreous or preretinal hemorrhage
795 preventing adequate visualization of the fundus to assess NV status. An injection
796 is given. PRP should not be given.
797

798 • **Failed/futile**

799 ○ Failure/futility criteria met. Decision to re-inject is at investigator discretion.
800 PRP may be given at this time (see below for cases that first require discussion
801 with the Protocol Chair or Coordinating Center designee), in which case the eye
802 will be considered a failure for analyses using PRP as an outcome.
803

804 ■ *Failure criteria are defined as*

805 1. *growth of NV or new NV of the retina, disc OR iris since the last*
806 *visit such that the NV, including fibrosis, is greater in extent than*

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

809
810 *OR*

811
812 *2. New or worsened NV of the angle* has developed since the last*
813 *visit. The investigator may perform PRP.*

814
815 *OR*

816
817 *3. definite worsening of NV or fibrous proliferation of the retina, disc*
818 *OR iris at least 1 day after the last injection that the investigator*
819 *believes is likely to lead to substantial vision loss if PRP is not*
820 *performed within 1 week. PRP may only be performed after*
821 *discussion with and approval from the Protocol Chair or*
822 *Coordinating Center designee.*

823
824 *▪ Futility criteria are defined as continued persistence or recurrence of NV*
825 *at 1.5 years or later follow-up that is equal to or greater than the extent of*
826 *the NV present at baseline and at least 5 study injections performed over*
827 *the preceding 6 months. PRP may only be performed after discussion with*
828 *and approval from the Protocol Chair or Coordinating Center designee.*
829

830 **4.2.3 Next Retreatment Evaluation**

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

836 **4.3 Panretinal Photocoagulation Treatment During Follow-up**

837 **Prompt PRP Group**

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

845
846 Alternative treatment (e.g. anti-VEGF) for PDR is only permitted in this group if neovascular
847 glaucoma has developed following completion of PRP. Otherwise, alternative treatment may
848 only be performed after discussion with and approval from the Protocol Chair or Coordinating
849 Center designee.

850 851 **Ranibizumab Plus Deferred PRP Group**

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

854 met starting after the first injection. If the investigator believes PRP is warranted prior to
855 meeting failure/futility criteria for PDR, the Protocol Chair or Coordinating Center designee
856 must be contacted for approval. See section 4.6 for details regarding PRP procedure. Once PRP
857 is given in the deferred group, further treatment for PDR is at investigator discretion.
858

859 **4.3.1 Deferral of Additional Scatter Photocoagulation for Decreased Visual Acuity from** 860 **Exacerbation of Macular Edema**

861 Before the completion of each PRP sitting, visual acuity testing should be completed using usual
862 care methods. If the usual care visual acuity is decreased from baseline acuity by 10 or more
863 letters (2 or more lines), a study protocol refraction and E-ETDRS best corrected visual acuity
864 should be completed (unless the decrease is due to vitreous hemorrhage). An OCT is to be
865 performed if the E-ETDRS best corrected visual acuity is decreased from baseline acuity by 10
866 or more letters.
867

868 Dilated ophthalmoscopic examination should be carried out to determine that the decreasing
869 vision is not secondary to vitreous hemorrhage. If vitreous hemorrhage is the cause of decreased
870 vision, appropriate scatter therapy for proliferative diabetic retinopathy should continue. If
871 proliferative diabetic retinopathy and vitreous hemorrhage are not responsible for the decreased
872 vision, PRP still should be carried out whenever possible. However, if the investigator believes
873 that exacerbation of macular edema is the cause of the decreased vision, at the investigator's
874 discretion, additional scatter photocoagulation can be deferred for two weeks.
875

876 If treatment is deferred because of exacerbation of macular edema, a two-week follow up visit
877 should be scheduled. Visual acuity (with study protocol refraction if 10 or more letters worse
878 than baseline) and OCT are repeated. Continuation of the scatter photocoagulation should be
879 considered and in general is appropriate even if there is a decrease in visual acuity. However, if
880 the visual acuity remains decreased by 10 or more letters and this decrease is secondary to
881 macular edema, the investigator may again defer completion of scatter treatment for an
882 additional two weeks and repeat the process again.
883

884 **4.3.2 Additional Scatter Photocoagulation for Proliferative Diabetic Retinopathy**

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

890 **4.4 Treatment for Diabetic Macular Edema**

891 This section describes use of study intravitreal ranibizumab and or focal/grid laser to treat
892 concurrent DME, when indicated. Non-study anti-VEGF drugs or alternative treatments (e.g.
893 corticosteroids) are not to be used to treat DME unless otherwise indicated below.
894

895 If central subfield-involved DME is present at baseline on OCT (central subfield thickness ≥ 250
896 microns on Zeiss Stratus or equivalent thickness on spectral domain OCT machine, within 8 days
897 of randomization) and visual acuity is ≤ 78 (20/32 or worse), intravitreal ranibizumab must be
898 given.
899

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

906
907 If treatment for DME is warranted, guidelines for intravitreal ranibizumab retreatment are
908 described in section 4.4.1 and for focal/grid photocoagulation in section 4.4.2. See section 4.5
909 for details regarding study drug and injection procedure. See section 4.7 for details regarding
910 focal/grid photocoagulation procedure.

911 912 **4.4.1 Intravitreal Injection Retreatment Guidelines for DME**

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

918
919 Once intravitreal ranibizumab is initiated for DME, it is recommended that the study eye receive
920 a series of study ranibizumab injections 4 weeks apart for 12 weeks (if the eye has already
921 received 4 consecutive injections for PDR over the course of the previous 4 months, this may be
922 skipped or reduced to total 4 consecutive injections).

923
924 At the next two 4-week interval visits, the eye may be evaluated for intravitreal injection
925 retreatment based on visual acuity and central subfield thickness on OCT.

926
927 *Note: all OCT values referenced below are on Zeiss Stratus; spectral domain equivalent may be*
928 *used.*

929
930 Each eye with no contraindication to additional injections may be categorized into one of the
931 following 2 categories:

- 932
- 933 • If the visual acuity letter score is ≥ 84 (20/20 or better) or the OCT central subfield
934 thickness is < 250 microns on Zeiss Stratus (or equivalent thickness on spectral domain
935 OCT machine), the decision to reinject is at investigator discretion. If an injection is not
936 given, treatment for DME other than focal/grid photocoagulation cannot be given. In
937 general, if both the visual acuity letter score is ≥ 84 and OCT central subfield thickness is
938 < 250 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT
939 machine), the injection should be deferred.
 - 940 • If the visual acuity letter score is < 84 (worse than 20/20) and OCT central subfield
941 thickness ≥ 250 microns on Zeiss Stratus (or equivalent thickness on spectral domain
942 OCT machine), an injection should be given.

943
944 At and after approximately 24 weeks from the initial study ranibizumab injection for DME, each
945 eye with no contraindication to additional injections may be categorized into one of the
946 following 4 categories:

947

- 948 1) *Visual acuity letter score ≥ 84 (20/20 or better) or OCT central subfield thickness < 250*
949 *microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine):*
950 • Decision to reinject is at investigator discretion. If an injection is not given, treatment
951 for DME other than focal/grid photocoagulation cannot be given. In general, if both
952 the visual acuity letter score is ≥ 84 and OCT central subfield thickness is < 250
953 microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine),
954 the injection should be deferred.
955
- 956 2) *Visual acuity score < 84 (worse than 20/20), OCT central subfield thickness ≥ 250*
957 *microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), and*
958 *evidence of improvement since the last injection:*
959 *Improvement is defined as either OCT central subfield thickness decreased by*
960 *10% or more OR visual acuity letter score has improved 5 or more.*
961 • An injection should be given.
962
- 963 3) *Failure/Futility Criteria Met*
964 *Failure/futility is defined as: VA letter score < 84 , OCT CSF ≥ 250 microns on*
965 *Zeiss Stratus (or equivalent thickness on spectral domain OCT machine), DME*
966 *present on clinical exam that is the cause of the visual loss, complete laser has*
967 *been given*
968 *AND*
969 *No improvement since the visit at which (or following which) the last laser*
970 *treatment was given, defined as OCT central subfield thickness decreased by*
971 *$< 10\%$ (or increased) AND visual acuity letter score improved by < 5 letters [or*
972 *worsened)*
973 *AND*
974 *Either 1) VA 10 or more worse than the initial study ranibizumab injection and*
975 *≥ 13 weeks since last laser treatment OR 2) ≥ 1 year since first study injection for*
976 *DME and 29 weeks since last laser:*
977 • The eye can be treated for DME at investigator discretion. Non-study anti-VEGF
978 drugs or alternative treatments may be given if the eye has already received at least 6
979 study ranibizumab injections. If feasible, Protocol Chair or Coordinating Center
980 designate approval should be obtained before administering a treatment that has not
981 been FDA approved for DME.
982
- 983 4) *Visual acuity score < 84 (worse than 20/20), OCT central subfield thickness ≥ 250*
984 *microns on Zeiss Stratus (or equivalent thickness on spectral domain OCT machine),*
985 *failure/futility criteria (see #3) not met, and no improvement since the last injection:*
986 *No improvement is defined as OCT central subfield thickness not decreased by at*
987 *least 10% AND visual acuity letter score not improved by at least 5.*
988 • Decision to reinject is at investigator discretion. In general, it is expected that an
989 injection will be given if there is edema to treat. If an injection is not given, treatment
990 for DME other than focal/grid photocoagulation cannot be given.
991

992 **4.4.2 Focal/Grid Photocoagulation Treatment for DME during Follow-Up**

993 Focal/grid photocoagulation may be given in lieu of intravitreal ranibizumab if DME develops
994 during follow-up for which the investigator believes intravitreal ranibizumab is not indicated.
995

996 If intravitreal ranibizumab is given at baseline or judged indicated during follow-up, it is
997 recommended that no focal/grid photocoagulation be given prior to 24 weeks from initial
998 ranibizumab injection for DME. After 24 weeks of intravitreal ranibizumab treatment, if the
999 OCT central subfield thickness has decreased by less than 10% (or has increased) and visual
1000 acuity letter score has improved by less than 5 (or has worsened) from the last 2 consecutive
1001 injections and between the last 2 consecutive injections, and the investigator believes that
1002 macular edema is present for which focal photocoagulation is indicated, it is recommended that
1003 the eye receive focal/grid photocoagulation.

1004
1005 Once focal/grid photocoagulation has been performed during the study, it is recommended that
1006 focal/grid photocoagulation be given within 10 days following each intravitreal injection for
1007 DME (or at the time of the visit if an injection is not given) unless one of the following is present
1008 at the time of the injection:

- 1009 • Focal/grid laser given in the previous 13 weeks
- 1010 • Complete focal/grid laser has already been given in the investigator’s judgment. Both of
1011 the following criteria must be met to be considered “complete” laser:
 - 1012 ○ All leaking microaneurysms within areas of retinal thickening or contributing to
1013 the edema that is threatening the center of the macula have been directly treated at
1014 some time with laser burns directly over the microaneurysms
 - 1015 ○ All other areas of current retinal thickening have been treated with laser burns
1016 (either focal or grid), such that the laser burns are “on average” within 100
1017 microns of each other (range between 50 and 150 microns) in a grid pattern
1018 throughout the area of retinal thickening
- 1019 • The central subfield thickness is <250 microns and there is no edema threatening the
1020 fovea (i.e., edema within 500 microns of the foveal center, or edema associated with lipid
1021 within 500 microns of the foveal center or 1 disc area of edema within 1 disc area of the
1022 foveal center).

1024 **4.4.3 Next Retreatment Evaluation**

1025 Follow-up visits for DME treatment may occur at 4, 8, or 16-week intervals, as needed. It is
1026 recommended that follow-up visits occur every 4 weeks for the first year from initial
1027 ranibizumab treatment for DME. After the first year, if the injection is deferred for both DME
1028 treatment and PDR treatment (see Section 4.2) at the current and previous 2 visits, the next study
1029 follow-up visit is recommended in twice the time since the last visit up to a maximum of 16
1030 weeks between visits. Otherwise, the next study follow-up visit should be in 4 weeks.

1032 **4.5 Ranibizumab (Lucentis™)**

1033 Ranibizumab (Lucentis™) is made by Genentech, Inc. and is approved by the FDA for the
1034 treatment of age-related macular degeneration and macular edema secondary to retinal vein
1035 occlusion, and approved by the European Medicines Agency and other regulatory authorities
1036 outside of the United States for DME.

1037
1038 Study eyes assigned to receive ranibizumab will receive a dose of 0.5mg in 0.05cc. The
1039 physical, chemical, and pharmaceutical properties and formulation of ranibizumab are provided
1040 in the Clinical Investigator’s Brochure.

1041

1042 **4.5.1 Intravitreal Injection Technique**

1043 The injection is preceded by a povidone iodine prep of the conjunctiva. Antibiotics in the pre-,
1044 peri-, or post-injection period are not necessary but can be used at investigator discretion if such
1045 use is part of his/her usual routine.

1046
1047 The injection will be performed using sterile technique. The full injection procedure is described
1048 in the protocol-specific study procedures manual.

1049
1050 **4.5.2 Deferral of Injections Due to Pregnancy**

1051 Female study participants must be questioned regarding the possibility of pregnancy prior to
1052 each injection. In the event of pregnancy, study injections must be discontinued.

1053
1054 **4.5.3 Delay in Giving Injections**

1055 If a scheduled injection is not given by the end of the visit window, it can still be given up to 1
1056 week prior to the next visit window opening. If it is not given by that time, it will be considered
1057 missed.

1058
1059 If an injection is given late, the next scheduled injection should occur no sooner than 3 weeks (21
1060 days) after the previous injection.

1061 **4.6 Panretinal Photocoagulation Technique**

1062 Study eyes that receive panretinal photocoagulation (prompt PRP eyes at baseline or deferred
1063 PRP eyes that meet failure/futility criteria detailed in section 4.2.2) should have 1200 to 1600
1064 burns with a spot size on the retina of approximately 500 microns (or the equivalent area treated
1065 with a PASCAL) given over 1 to 3 sittings and completed within 8 weeks (56) days of initiation.

1066
1067 The burn characteristics for non-automated photocoagulation will be as follows:
1068

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

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

1069
1070 An anesthetic injection (retrobulbar, peribulbar or sub-Tenon's) can be used at investigator
1071 discretion.

1072
1073 An indirect laser approach can be used at investigator discretion.

1074
1075 If a laser is used that has the capability of producing an automated pattern (e.g. the PASCAL),
1076 the automated pattern producing mode is permissible. Guidelines for use of the automated
1077 pattern are included in the study procedure manual.

1078 **4.7 Focal/Grid Photocoagulation Technique**

1079 If focal/grid photocoagulation is warranted, the laser treatment 'session' should generally be
1080 completed in a single 'sitting'. The photocoagulation treatment technique, as described below, is
1081 a modification of the ETDRS technique and is the treatment approach that is commonly used in
1082 clinical practice. Use of fluorescein angiography to direct the treatment is at the discretion of the
1083 investigator. Laser treatment following an injection, if needed, will be based on the pre-injection
1084 macular appearance.
1085

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

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

1086 *Additional guidelines for performing laser treatment using the PASCAL are included in the
1087 Procedure Manual.

1088

1089 *Note:*

1090 • *The investigator may choose any laser wavelength for photocoagulation within the green to*
1091 *yellow spectrum. The wavelength used will be recorded.*

1092 • *Lenses used for the laser treatment cannot increase or reduce the burn size by more than*
1093 *10%. The study procedure manual contains a listing of acceptable lenses.*

1094
1095
1096

**CHAPTER 5.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP**

1097 **5.1 Endophthalmitis**

1098 Diagnosis and treatment of endophthalmitis is based on investigator’s judgment. Obtaining
1099 cultures of vitreous and aqueous fluid is highly recommended prior to initiating antibiotic
1100 treatment for presumed endophthalmitis.

1101 **5.2 Surgery for Vitreous Hemorrhage, Traction Detachment, and Other Complications of**
1102 **Diabetic Retinopathy**

1103 A study eye could develop a vitreous hemorrhage or traction detachment that may cause visual
1104 impairment. In these cases, vitrectomy may be performed at the discretion of the investigator;
1105 however, vitrectomy for hemorrhage alone should not be scheduled for at least 8 weeks after
1106 onset of hemorrhage without first discussing with the Protocol Chair or Coordinating Center
1107 designee.

1108 **5.3 Treatment of Macular Edema in Nonstudy Eye**

1109 Treatment of DME in the nonstudy eye is at investigator discretion.

1110 **5.4 Diabetes Management**

1111 Diabetes management is left to the study participant’s medical care provider.

1112 **5.5 Study Participant Withdrawal and Losses to Follow-up**

1113 A study participant has the right to withdraw from the study at any time. If s/he is considering
1114 withdrawal from the study, the principal investigator should personally speak to the individual
1115 about the reasons, and every effort should be made to accommodate the study participant to
1116 allow continued participation if possible.

1117
1118 The goal for the study is to have as few losses to follow-up as possible. The Coordinating Center
1119 will assist in the tracking of study participants who cannot be contacted by the site. The
1120 Coordinating Center will be responsible for classifying a study participant as lost to follow-up.

1121
1122 Study participants who withdraw will be asked to have a final closeout visit at which the testing
1123 described for the protocol visits will be performed. Study participants who have an adverse
1124 effect attributable to a study treatment or procedure will be asked to continue in follow-up until
1125 the adverse event has resolved or stabilized.

1126
1127 Study participants who withdraw or are determined to have been ineligible post-randomization
1128 will not be replaced.

1129 **5.6 Discontinuation of Study**

1130 The study may be discontinued by the Executive Committee (with approval of the Data and
1131 Safety Monitoring Committee) prior to the preplanned completion of follow-up for all study
1132 participants.

1133 **5.7 Contact Information Provided to the Coordinating Center**

1134 The Coordinating Center will be provided with contact information for each study participant.

1135 Permission to obtain such information will be included in the Informed Consent Form. The
1136 contact information may be maintained in a secure database and will be maintained separately
1137 from the study data.

1138
1139 Phone contact from the Coordinating Center will be made with each study participant in the first
1140 month after enrollment. Additional phone contacts from the Coordinating Center will be made if
1141 necessary to facilitate the scheduling of the study participant for follow-up visits. A study
1142 participant-oriented newsletter will be sent at least twice a year. A study logo item may be sent
1143 once a year.

1144
1145 Study participants will be provided with a summary of the study results in a newsletter format
1146 after completion of the study by all study participants.

1147 **5.8 Study Participant Reimbursement**

1148 The study will be paying the study participant \$50 for baseline and each completed annual
1149 protocol visit and \$25 per completed non-annual protocol visit to cover travel and other visit-
1150 related expenses. Payment will be made from the Coordinating Center. Additional travel
1151 expenses will be paid in select cases for study participants with higher expenses.

1152 **CHAPTER 6.**
1153 **ADVERSE EVENTS**
1154

1155 **6.1 Definition**

1156 An adverse event is any untoward medical occurrence in a study participant, irrespective of
1157 whether or not the event is considered treatment-related. An adverse event can therefore be any
1158 unfavorable and unintended sign (including an abnormal lab finding), symptom or disease
1159 temporally associated with the use of the treatment, whether or not related to the treatment. This
1160 includes preexisting medical conditions (other than the condition being studied) judged by the
1161 investigator to have worsened in severity or frequency or changed in character.

1162 **6.2 Recording of Adverse Events**

1163 Throughout the course of the study, all efforts will be made to remain alert to possible adverse
1164 events or untoward findings. The first concern will be the safety of the study participant, and
1165 appropriate medical intervention will be made.
1166

1167 All adverse events whether volunteered by the subject, discovered by study personnel during
1168 questioning, or detected through physical examination, laboratory test, or other means will be
1169 reported on an adverse event form online. Each adverse event form is reviewed by the
1170 Coordinating Center to verify the coding and the reporting that is required.
1171

1172 The study investigator will assess the relationship of any adverse event to be related or unrelated
1173 by determining if there is a reasonable possibility that the adverse event may have been caused
1174 by the treatment.
1175

1176 To ensure consistency of adverse event causality assessments, investigators should apply the
1177 following general guideline when determining whether an adverse event is related:
1178

1179 **Yes**

1180 There is a plausible temporal relationship between the onset of the adverse event and
1181 administration of the study treatment, and the adverse event cannot be readily explained by the
1182 subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event
1183 follows a known pattern of response to the study treatment; and/or the adverse event abates or
1184 resolves upon discontinuation of the study treatment or dose reduction and, if applicable,
1185 reappears upon re-challenge.
1186

1187 **No**

1188 Evidence exists that the adverse event has an etiology other than the study treatment (e.g.,
1189 preexisting medical condition, underlying disease, intercurrent illness, or concomitant
1190 medication); and/or the adverse event has no plausible temporal relationship to study treatment
1191 administration (e.g., cancer diagnosed 2 days after first dose of study drug).
1192

1193 The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3)
1194 severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse
1195 event is not necessarily serious. For example, itching for several days may be rated as severe,
1196 but may not be clinically serious.
1197

1198 Adverse events will be coded using the MedDRA dictionary.

1199

1200 Definitions of relationship and intensity are listed on the DRCRnet website data entry form.

1201

1202 Adverse events that continue after the study participant's discontinuation or completion of the
1203 study will be followed until their medical outcome is determined or until no further change in the
1204 condition is expected.

1205 **6.3 Reporting Serious or Unexpected Adverse Events**

1206 A serious adverse event is any untoward occurrence that:

1207 • Results in death

1208 • Is life-threatening; (a non life-threatening event which, had it been more severe, might have
1209 become life-threatening, is not necessarily considered a serious adverse event)

1210 • Requires inpatient hospitalization or prolongation of existing hospitalization

1211 • Results in persistent or significant disability/incapacity or substantial disruption of the ability
1212 to conduct normal life functions (sight threatening)

1213 • Is a congenital anomaly/birth defect

1214 • Is considered a significant medical event by the investigator based on medical judgment (e.g.,
1215 may jeopardize the participant or may require medical/surgical intervention to prevent one of
1216 the outcomes listed above)

1217

1218 Unexpected adverse events are those that are not identified in nature, severity, or frequency in
1219 the current Lucentis® Clinical Investigator's Brochure.

1220

1221 Serious or unexpected adverse events must be reported to the Coordinating Center immediately
1222 via completion of the online serious adverse event form.

1223

1224 The Coordinating Center will notify all participating investigators of any adverse event that is
1225 both serious and unexpected. Notification will be made within 10 days after the Coordinating
1226 Center becomes aware of the event.

1227

1228 Each principal investigator is responsible for informing his/her IRB of serious study-related
1229 adverse events and abiding by any other reporting requirements specific to their IRB.

1230 **6.4 Data and Safety Monitoring Committee Review of Adverse Events**

1231 A Data and Safety Monitoring Committee (DSMC) will advise the Coordinating Center
1232 regarding the protocol, template informed consent form, and substantive amendments and will
1233 provide independent monitoring of adverse events. Cumulative adverse event data are semi-
1234 annually tabulated for review by the DSMC. Following each DSMC data review, a summary
1235 will be provided to institutional review boards. A list of specific adverse events to be reported to
1236 the DSMC expeditiously, if applicable, will be compiled and included as part of the DSMC
1237 Standard Operating Procedures document.

1238

1239 **6.5 Risks**

1240 **6.5.1 Ranibizumab**

1241 Ranibizumab is well tolerated in people. More than 5000 study participants have been treated
1242 with injections of ranibizumab in clinical studies to date, however the full safety profile with
1243 long-term injections is not yet known. Some participants in ongoing clinical studies have
1244 developed inflammation in the eye (uveitis) which can be treated with anti-inflammatory drops.
1245 Increased eye pressure leading to glaucoma or cataract has also resulted from injections of
1246 ranibizumab. Other ocular adverse events that have occurred in ongoing clinical studies are
1247 believed to be due to the intravitreal injection itself and not the study drug. These are listed in
1248 section 6.5.2.

1249
1250 Some study participants have experienced systemic adverse events that may possibly be related
1251 to ranibizumab. Until cumulative safety data are analyzed, precise incidence figures are
1252 unknown and a causal relationship cannot be ruled out. These include arterial thromboembolic
1253 events and onset of hypertension. In a phase IIIb study to evaluate the long-term safety and
1254 efficacy of ranibizumab (The Safety Assessment of Intravitreal Lucentis for AMD, or SAILOR
1255 trial), which randomized patients with wet age-related macular degeneration to 0.5 mg
1256 ranibizumab or 0.3 mg ranibizumab, there was a higher rate of cerebrovascular stroke in the
1257 group that received the higher drug dose (1.2 vs 0.7%), although this trend did not achieve
1258 statistical significance.⁴³ It appeared that patients who had a prior history of stroke may be at
1259 greater risk for having a stroke after receiving ranibizumab, although there was a low incidence
1260 of stroke overall in this group. Additional data regarding systemic safety of ranibizumab in a
1261 diabetic population is also available from the DRCR.net Protocol I primary results.³⁶ This study
1262 enrolled a combined total of 375 patients in the two ranibizumab arms, who received an average
1263 of 8-9 intravitreal injections of 0.5 mg ranibizumab over the first year of treatment. There was
1264 no indication of an increased risk of cardiovascular or cerebrovascular events in the
1265 ranibizumab-treated study participants as compared with the triamcinolone-treated study
1266 participants or study participants who received no intravitreal drug. Indeed, lower rates of
1267 cardiovascular events as defined by the Antiplatelet Trialists' Collaboration were seen in the
1268 ranibizumab groups as compared with the sham group at both one (3% vs 8%) and two (5% vs
1269 12%) years. Furthermore, a retrospective cohort study of 146,942 Medicare beneficiaries who
1270 received treatment for age-related macular degeneration did not find an increased risk of
1271 mortality, myocardial infarction, bleeding, or stroke from ranibizumab compared with laser
1272 therapy.⁴⁴

1273 There may be side effects and discomforts that are not yet known.

1274
1275 Long-term studies in animals have not been performed to evaluate the carcinogenic potential of
1276 ranibizumab or its effect on fertility.

1277 **6.5.2 Potential Adverse Effects of Intravitreal Injection**

1278 Rarely, the drugs used to anesthetize the eye before the study drug injections (proparacaine,
1279 tetracaine, or xylocaine) can cause an allergic reaction, seizures, and an irregular heartbeat.

1280
1281 Subconjunctival hemorrhage or floaters will commonly occur as a result of the intravitreal
1282 injection. Discomfort, redness, or itching lasting for a few days is also likely.

1283
1284 Immediately following the injection, there may be elevation of intraocular pressure. It usually
1285 returns to normal spontaneously, but may need to be treated with topical drugs or a

1286 paracentesis to lower the pressure. The likelihood of permanent loss of vision from elevated
1287 intraocular pressure is less than 1%.

1288
1289 As a result of the injection, endophthalmitis (infection in the eye) could develop. If this occurs, it is
1290 treated by intravitreal injection of antibiotics, but there is a risk of permanent loss of vision including
1291 blindness. The risk of endophthalmitis is less than 1%.

1292
1293 As a result of the injection, a retinal detachment could occur. If this occurs, surgery may be
1294 needed to repair the retina. The surgery is usually successful at reattaching the retina.
1295 However, a retinal detachment can produce permanent loss of vision and even blindness. The
1296 risk of retinal detachment is less than 1%.

1297
1298 The injection could cause a vitreous hemorrhage. Usually the blood will resolve
1299 spontaneously, but if not, surgery may be needed to remove the blood. Although the surgery
1300 usually successfully removes the blood, there is a small risk of permanent loss of vision and
1301 even blindness. The risk of having a vitreous hemorrhage due to the injection is less than 1%.

1302 **6.5.3 Risks of Focal/Grid Photocoagulation Treatment**

1303 Serious complications from laser treatment are rare. They occur in fewer than 1 in 1,000 cases.
1304 These include damage to the macula, bleeding inside the eye, immediate or delayed increase in
1305 pressure inside the eye, damage to the optic nerve, damage to the iris, damage to the lens or an
1306 intraocular lens, retinal hole, blindness, and loss of the eye. If a laser burn occurs too near the
1307 center of vision, a scotoma could develop. After several years, the scars caused by the laser may
1308 enlarge and may be associated with vision loss.

1309
1310 Anesthetic drops and a contact lens may be used as a part of the laser procedure. Risks include
1311 allergic reaction, infection, and corneal abrasion (scratch on the clear front surface of the eye). If
1312 any of these problems occur, they usually clear up rapidly.

1313 **6.5.4 Risks of Panretinal Photocoagulation Treatment**

1314 Panretinal photocoagulation can reduce peripheral and night vision. In addition, it can reduce
1315 transient or permanent central vision loss. Rarely, it can cause transient increase in intraocular
1316 pressure, presumably through secondary angle closure as the lens-iris diaphragm shifts forward
1317 with transient swelling of the posterior tissues.

1318
1319 In some cases retrobulbar or peribulbar injection may be used to anesthetize the eye and to
1320 reduce eye movements. Complications of retrobulbar and peribulbar injections are rare. They
1321 include, but are not limited to, the following: retrobulbar hemorrhage (bleeding behind the
1322 eyeball); perforation of the eye by the needle; damage to the optic nerve; diplopia lasting up to
1323 24 hours or more; ptosis lasting up to 24 hours or more; difficulty speaking or breathing;
1324 lightheadedness/syncope/vasovagal response; allergy to any components of the injection; life
1325 threatening response due to the spread of anesthesia to the brain stem, resulting in seizures,
1326 drowsiness, confusion, loss of ability to talk, convulsions, stoppage of breathing, or stoppage of
1327 heartbeat. All of these complications are rare.

1328 **6.5.5 Risks of Eye Examination and Tests**

1329 There is a rare risk of an allergic response to the topical medications used to anesthetize the eye
1330 or dilate the pupil. Dilating drops rarely could cause an acute angle closure glaucoma attack, but

1331 this is highly unlikely since the study participants in the study will have had their pupils dilated
1332 many times previously.

1333

1334 There are no known risks associated with OCT or fundus photographs. The bright flashes used
1335 to take the photographs may be annoying, but are not painful and cause no damage.

1336
1337
1338
1339

CHAPTER 7. STATISTICAL METHODS

1340 The approach to sample size and statistical analyses are summarized below. A detailed statistical
1341 analysis plan will be written and finalized prior to the completion of the study. The analysis plan
1342 synopsis in this chapter contains the framework of the anticipated final analysis plan.
1343

1344

7.1 Sample Size

1345 The sample size estimate has been computed for the primary study objective, to determine
1346 whether visual acuity in the deferred PRP group is non-inferior to visual acuity in the prompt
1347 PRP group at 2 years. The primary analysis consists of a two-group comparison of mean change
1348 in visual acuity at 2 years, adjusted for baseline.

1349

7.1.1 Sample Size Assumptions

1350 For the cohort without center involved DME, the 2-year visual acuity outcomes for the prompt
1351 PRP group can be estimated using unpublished data from the ETDRS for eyes without center
1352 involved thickening on baseline photographs, with PDR on baseline photographs (level 61, 65),
1353 baseline visual acuity letter score ≥ 24 that were assigned to the full scatter group followed by
1354 focal/grid laser as needed (N=113). For the cohort with center involved DME, the 2-year visual
1355 acuity outcomes can be estimated using data from the ranibizumab groups in DRCR.net LRT for
1356 DME Study (Protocol I). Although the visual acuity and retinopathy severity status eligibility
1357 criteria differ between the current study and Protocol I, other key eligibility criteria between the
1358 two studies are the same. In addition, many eyes in Protocol I did have PDR although in that
1359 trial the investigator judged at baseline that the eye would not require PRP within 6 months.
1360 Therefore eyes in Protocol I with PDR at baseline may serve as the best available estimate for
1361 outcome rates in the current study for eyes with DME which will be treated with anti-VEGF.
1362

1363 Table 1 summarizes the 2 year data from both ETDRS cohort and the Protocol I cohort
1364 separately.
1365

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

1366
1367 The slightly more conservative estimates from DRCR.net were used for sample size estimation:

- 1368
- Standard deviation: 16 letters (95% C.I.: 14, 19)
 - Correlation: -0.21 (95% C.I.: 0, -0.38)
- 1369

1370

7.1.2 Non-Inferiority Margin

1371 The non-inferiority margin specifies how much worse the anti-VEGF plus deferred PRP group
1372 could be than the prompt PRP group in the population with respect to the primary change in
1373 visual acuity outcome yet still be considered to be non-inferior. If the upper bound of the one-
1374 sided confidence interval around the difference (prompt PRP group minus anti-VEGF plus
1375 deferred PRP group) is less than this margin, indicating that a true difference between the groups

1376 of a size equal to the margin (or larger) is unlikely, the anti-VEGF plus deferred PRP group will
1377 be considered non-inferior to the prompt PRP group.

1378
1379 Based on the objectives of this study and the potential deleterious effects on visual function by
1380 PRP, a non-inferiority margin of 5 letters was judged to be clinically acceptable. In addition, this
1381 margin is less than the lower limit of the 95% confidence interval for the comparison of
1382 immediate PRP with observation. This helps ensure that anti-VEGF with deferred PRP is
1383 superior to observation alone in the event that it is found to be non-inferior to prompt PRP.

1384 7.1.3 Sample Size Estimations

1385
1386 **Table 2: Sample Size Estimates Per Group using different parameters:**

1387 Alpha = 0.025, Power = 85%

1388

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

1389

1390 In estimating the sample size, the following assumptions have been made:

- 1391 • Standard deviation of change in letter score = 16
- 1392 • Correlation between baseline and change in visual acuity letter score = -0.21
- 1393 • Type 1 error rate = 0.025 (1-sided)
- 1394 • Power = 85%

1395

1396 With these assumptions, sample size has been calculated to be 177 eyes in each group. This
1397 sample size will be increased to 190 eyes per group (380 total eyes) to account for lost to
1398 follow-up. Assuming 20% of study participants have two study eyes (based on enrollment in
1399 previous DRCR.net studies), this equates with having approximately 316 study participants.

1400

1401 The primary analysis will adjust for correlation within study participants with two study eyes
1402 (projected to be 20% of the study participants); therefore, the actual power will be somewhat
1403 higher than 85%, depending on the degree of correlation and the number of study participants
1404 with two study eyes. In addition, since multiple imputation methods will be used for missing
1405 data at follow-up, as described below, the overall power may be increased above 85% since the
1406 sample size calculations include an adjustment for lost to follow-up.

1407 7.2 Efficacy Analysis Plan

1408 7.2.1 Principles for Analysis

1409 The primary analysis will consist of a comparison of change in visual acuity in the prompt PRP
1410 group with the ranibizumab+deferred PRP group at the 2-year follow-up visit, using analysis of
1411 covariance to adjust for baseline visual acuity and generalized estimating equations (GEE) to
1412 account for the correlation within study participants with two study eyes. If the upper bound of

1413 the one-sided 97.5% confidence interval on the difference in change in visual acuity between the
1414 two groups (prompt PRP group minus anti-VEGF plus deferred PRP group) lies below 5 letters,
1415 the null hypothesis that ranibizumab+deferred PRP is not non-inferior will be rejected at the
1416 0.025 level.

1417
1418 The primary analysis will include all randomized eyes, according to the treatment group
1419 assignment at randomization. Missing data and treatment deviations will be handled as follows:

- 1420 • For study participants who completed the 2-year visit and do not receive an alternate
1421 treatment for PDR, the 2-year data will be used.
 - 1422 ○ Note: this includes any patients who meet the criteria above but do not receive all
1423 injections of the randomized treatment required by the protocol.
- 1424 • For study participants who do not complete the 2-year visit and do not receive an
1425 alternate treatment, multiple imputation methods using all available data from
1426 Assessment Visits will be used to impute 2-year data.
- 1427 • For all other study participants, i.e. those who receive an alternate treatment, multiple
1428 imputation methods, using only data from the last Assessment Visit prior to the
1429 administration of the alternate treatment, will be used to impute 2-year data. This
1430 includes eyes in the deferred group who get PRP before indicated by protocol. PRP
1431 treatment per protocol, intravitreal ranibizumab, or focal/grid laser are not considered
1432 alternate treatments.

1433
1434 Secondly, a sensitivity analysis will be conducted as described above, except the 3rd group will
1435 be excluded. If the results of the two methods differ, exploratory analyses will be performed to
1436 evaluate the factors that have contributed to the differences.

1437
1438 The primary analysis will pool eyes with and without center involved DME at baseline.
1439 However, all analyses will be replicated in subgroups based on baseline central DME status.

1440
1441 Imbalances between groups in important covariates are not expected to be of sufficient
1442 magnitude to produce confounding. However, the presence of confounding will be evaluated in
1443 regression models by including the following baseline covariates related to the patient (age) and
1444 study eye (visual acuity, retinal thickening on OCT, presence of DME, and prior treatment for
1445 DME). Additional variables that are associated with the outcome will be included if there is an
1446 imbalance in the variables between groups.

1447
1448 Pre-planned subgroup analyses will be described in the detailed Statistical Analysis Plan and
1449 include stratification by presence of central-subfield involved DME, visual acuity, central
1450 subfield thickness, and prior DME treatment history. For eyes in which DME treatment was
1451 initiated, additional analyses will compare treatment group response rates based on adherence to
1452 the DRCR.net DME retreatment algorithm.

1453
1454 There are no data to suggest that the treatment effect will vary by gender or race/ethnicity.
1455 However, both of these factors will be evaluated in exploratory analyses.

1456
1457 Longitudinal analyses also will be conducted to assess trends over time.

1458
1459 The number of study participants per center is small for many centers, therefore center effects
1460 will not be included in the statistical model; however for centers with a large number of study

1461 participants, the treatment effect will be assessed. If a positive overall effect of treatment is
1462 found, heterogeneity of treatment effect across centers will be explored using random center
1463 effects.

1464
1465 All linear model assumptions will be verified including linearity, normality of residuals, and
1466 homoscedasticity. If model assumptions are not met a nonparametric analysis will be
1467 considered.

1468 **7.2.2 Secondary Outcomes for Treatment Group Comparison**

1469 1470 **7.2.2.1 Visual Acuity**

1471 Visual acuity is the primary outcome variable. As described earlier, the primary outcome is the
1472 mean change in visual acuity at 2 years adjusted for the baseline acuity.

1473
1474 Additional analyses will be conducted on the visual acuity data to assess for consistency with the
1475 primary analysis. The additional analyses will include the following:

1476
1477 Table 2. Additional Analyses of Visual Acuity

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

1478
1479
1480 **7.2.2.2 Visual Function Testing**
1481 Humphrey visual field testing (at select sites), NEI VFQ-25, and UAB-LLQ will be performed to
1482 assess visual function.

1483 1484 **Analysis of Visual Function Questionnaire Data**

1485 A treatment group comparison of change in visual function subscale scores from baseline to 2
1486 years (to coincide with the primary visual acuity outcome) will be performed using analysis of
1487 covariance with adjustment for baseline score. As visual function subscale scores are measured
1488 at the study participant level, data from bilateral participants is non-informative with respect to
1489 treatment effect; hence, bilateral participants will not be included in these analyses. The null
1490 hypothesis being tested will be the usual efficacy hypothesis of no difference in mean subscale
1491 score by treatment. To control for inflation in the type I error rate due to testing of multiple
1492 subscales, the following subscales that are hypothesized to be those most likely to differ by
1493 treatment group will be considered the primary subscales of interest: driving (NEI VFQ-25 and
1494 UAB-LLQ subscales), peripheral vision (NEI VFQ-25 single item and UAB-LLQ subscale),
1495 color vision (NEI VFQ-25 and UAB-LLQ single items), and general dim lighting (UAB-LLQ
1496 subscale). Evidence of a treatment difference on these scales will be interpreted as definitive
1497 evidence of a treatment group difference with respect to the subscale in question. To further

1498 control for multiple testing, only p-values less than 0.01 will be considered statistically
1499 significant evidence for a treatment difference.

1500
1501 All other subscales from the NEI-VFQ and UAB-LLQ will be analyzed similarly to the primary
1502 subscales; however, statistically significant differences on these subscales will be considered
1503 suggestive of treatment group differences rather than definitive. In addition to the analysis of 2
1504 year data, a longitudinal analysis of subscale scores that includes all annual visits will also be
1505 performed using linear mixed models to account for correlation within participant over time.
1506 The purpose of this analysis will be to determine whether there are significant trends over the 5
1507 years, and whether any treatment group differences identified at 2 years are consistently
1508 maintained throughout the 5 year follow up period.

1509 1510 **Analysis of Visual Field Testing Data**

1511 A treatment group comparison of total point score will be performed using the same analysis
1512 methods proposed for the visual function subscale scores. Bilateral participants will be included
1513 in these analyses. The central (30 degree) and peripheral (30-60 degree) fields will be analyzed
1514 combining both fields, and also analyzed separately.

1515 1516 **7.2.2.3 Diabetic Retinopathy Outcomes**

1517 The treatment groups will be compared on the following key diabetic retinopathy outcomes of
1518 interest at the 2 year visit:

- 1519
- 1520 • Need for supplemental PRP after completion of initial deferred or prompt PRP
 - 1521 • Need for vitrectomy
 - 1522 • Development of neovascular glaucoma
 - 1523 • Percent of eyes with vitreous hemorrhage
 - 1524 • Proportion of eyes with complete regression of neovascularization on fundus
1525 photography

1526
1527 Binary outcomes will be analyzed using logistic regression models and GEE to account for the
1528 potential correlation between two study eyes.

1529
1530 Within the ranibizumab+deferred PRP group the following outcome will be assessed. 95%
1531 confidence intervals will be constructed.

- 1532 • Proportion of eyes not requiring PRP by 2 years.

1533 1534 **7.2.2.4 Macular Thickness**

1535 Retinal thickening outcomes will be assessed from the OCT central subfield and retinal volume.
1536 For each eye, the change in central subfield OCT retinal thickness and change in retinal volume
1537 from baseline will be computed. A treatment group comparison on the following outcomes will
1538 be performed:

- 1539 • Change in OCT central subfield thickness
- 1540 • Change in OCT retinal volume
- 1541 • Proportion of eyes with OCT central subfield thickness of $\geq 250 \mu\text{m}$ on Stratus OCT (or
1542 standard deviation equivalent) and at least a $25 \mu\text{m}$ increase from baseline

1543
1544 Binary outcomes will be analyzed using logistic regression models adjusting for baseline factors
1545 where appropriate and GEE to account for the correlation between two study eyes. Continuous

1546 outcomes will be analyzed using an analysis of covariance model adjusting for baseline measures
1547 where appropriate and GEE to account for the potential correlation between two study eyes.
1548

1549 **7.2.2.5 Economic Analysis**

1550 The purpose of the economic analysis is to compare the treatment groups with respect to cost,
1551 cost consequences, and cost utility. The viewpoint adopted is that of a third party payer. For the
1552 cost-consequence and cost-utility analyses we have adopted a perspective that includes patient
1553 and broader societal issues, particularly focusing on workplace productivity loss.
1554

1555 **Cost Consequence Analysis**

1556 Data from the clinical trial on number of clinic visits completed, number of procedures
1557 performed (e.g. OCT, fundus photographs), number of PRP treatments, and number of
1558 ranibizumab treatments will be used to estimate an average cost per patient for each treatment
1559 arm, using the Medicare Fee Schedule to estimate medical costs. The cost estimates in
1560 combination with the data on functional outcomes and percent productivity loss (without
1561 applying a monetary value) for each treatment arm will be incorporated into a cost consequence
1562 analysis. While, in theory, the set of functional outcomes can all be subsumed by a health-
1563 related quality of life measure, we treat it as a cost-consequence analysis because there are
1564 specific elements of vision-related function that are important to track and to value individually
1565 against the costs of the intervention. For this analysis, the estimated average treatment group
1566 difference in costs is stated, with variation being characterized by variation in the quantity of
1567 services, which will be reported as a 95% confidence interval. In addition, we will state the
1568 observed treatment group differences in the functional outcomes and percent productivity loss
1569 and their 95% confidence intervals. This provides a summary of the functional benefits, if any,
1570 that are obtained with the more costly treatment. The functional outcomes of interest are
1571 differences by treatment group with respect to:

- 1572 • Proportion of participants driving at baseline who stopped driving wholly or partly due to
1573 vision
- 1574 • Proportion of participants driving at night at baseline who stopped driving at night wholly
1575 or partly due to vision
- 1576 • Mean change from baseline in NEI VFQ-25 driving subscale score
- 1577 • Mean change in UAB-LLQ driving subscale score
- 1578 • Mean change in UAB-LLQ general dim lighting subscale score
- 1579 • Mean change in NEI VFQ-25 peripheral vision subscale score
- 1580 • Mean change in UAB-LLQ peripheral vision subscale score
- 1581 • Mean change in NEI VFQ-25 color vision subscale score
- 1582 • Mean change in UAB-LLQ color vision subscale score
- 1583 • Mean change in percent work time missed due to vision problems over the past week
- 1584 • Mean change in percent impairment while working due to vision problems over the past
1585 week
- 1586 • Mean change in percent overall work impairment due to vision problems over the past
1587 week
- 1588 • Proportion of participants losing 10 or more letters of visual acuity
- 1589 • Difference in percent of productivity loss of subjects as measured by the WPAI
1590

1591 For functional outcomes measured at the participant level, data from bilateral participants is non-
1592 informative with respect to the treatment comparison and will not be included in the analyses.
1593 For outcomes measured at the eye level, data from bilateral participants will be included.
1594 Estimates of treatment effect will be adjusted for baseline level of the outcome. The cost
1595 consequence analysis will be conducted based on 1 year and 2 year data for all outcomes. In
1596 addition, the cost consequences with respect to the work outcomes will be calculated for each
1597 work outcome assessment visit and at 4 weeks from randomization.
1598

1599 **Cost Utility Analysis**

1600 Data from the time trade-off questionnaire will be used to calculate patient-level preferences for
1601 vision at baseline and each annual follow-up visit and to derive a quality-adjusted life year
1602 (QALY) measurement for each patient at these time points. The change from baseline will be
1603 calculated for each patient and averaged by treatment group adjusting for baseline using analysis
1604 of covariance. Only unilateral participants will be included in the analysis. The difference in
1605 average medical care costs for each treatment group divided by the difference by treatment group
1606 in the average change in QALY score from baseline will form the estimated incremental cost
1607 utility ratio (ICUR). The uncertainty in the estimate of the incremental cost-utility ratio will be
1608 represented by bootstrapping the analysis and repeating the incremental cost-utility calculation
1609 with each bootstrapped dataset. The bootstrapped incremental costs and incremental effects can
1610 be graphed in a plane or represented as a cost-effectiveness acceptability curve.
1611

1612 While there is debate over whether to include measures of productivity as part of the cost in a
1613 cost-effectiveness or cost-utility analysis, we have the option of including the monetized value of
1614 productivity loss as captured by the Workplace Productivity and Activity Impairment instrument.
1615 Including costs in the numerator of the cost-effectiveness ratio may be relevant if a more intense
1616 treatment requires a significant time commitment, which is useful to capture. Alternatively, if
1617 there is a substantial change in individuals' productivity as a result of treatment, an analysis can
1618 be done to determine whether the increase in productivity is sufficient to offset the cost of the
1619 more expensive treatment. We can use a non-parametric test to compare costs with costs saved.

1620 **7.2.3 Safety Analysis Plan**

1621 Adverse events will be categorized as study eye, non-study eye, and systemic. The events will be
1622 tabulated separately for the two treatment groups. Adverse events of interest will include:

- 1623 • Injection-related: endophthalmitis, tractional retinal detachment, rhegmatogenous
1624 retinal detachments, retinal tears, cataract, intraocular hemorrhage
- 1625 • Ocular drug-related: inflammation, cataract, cataract surgery, increased intraocular
1626 pressure, new or worsening neovascular glaucoma, glaucoma medications, glaucoma
1627 surgery, new or worsening tractional retinal detachment, progression of tractional
1628 retinal detachment from extramacular to macular, new or worsening
1629 neovascularization of the iris
- 1630 • Systemic drug-related: hypertension, cerebrovascular events, and cardiovascular
1631 events as defined by the Antiplatelet Trialists' Collaboration
 - 1632 ○ *Systemic adverse events for participants with two study eyes will be evaluated*
1633 *separately from participants with one study eye.*

1634
1635 Further definitions of the events for analysis and the analytic approach will be provided in the
1636 detailed statistical analysis plan.

1637 **7.2.4 Additional Tabulations and Analyses**

1638 The following will be tabulated according to treatment group:

- 1639 • Baseline demographic and clinical characteristics
- 1640 • Visit completion rate for each visit
- 1641 • Protocol deviations

1642 **7.2.5 Interim Analysis Plan**

1643 A formal plan for interim analyses will be established in consultation with the DSMC.

1644

1645

CHAPTER 8. REFERENCES

1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691

1. Kempen JH, O`Colmain BJ, Leske MC, et al. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol.* 2004;122(4):552-63.
2. Aiello LP. Angiogenic pathways in diabetic retinopathy. *N Engl J Med.* 2005;353:839-41.
3. Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. *Ann Intern Med.* 1996;124(pt 2)(164-9).
4. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol.* 1976;81(4):383-96.
5. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed 10-13-09.
6. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol.* 1984;102:527-32.
7. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia.* 2001;44(2):156-63.
8. Ferris FL, 3rd, Davis MD, Aiello LM. Treatment of diabetic retinopathy. *N Engl J Med.* 1999;341(9):667-78.
9. Ferris F. Early photocoagulation in patients with either type I or type II diabetes. *Trans Am Ophthalmol Soc.* 1996;94:505-37.
10. Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol.* 2009;127(2):132-40.
11. Diabetic Retinopathy Clinical Research Network. Randomized Trial Evaluating Short-Term Effects of Intravitreal Ranibizumab or Triamcinolone Acetonide on Macular Edema Following Focal/Grid Laser for Diabetic Macular Edema in Eyes Also Receiving Panretinal Photocoagulation. *Retina* (Submitted for Publication). 2010.
12. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol.* 1985;103(12):1796-806.
13. McDonald HR, Schatz H. Macular edema following panretinal photocoagulation. *Retina.* 1985;5(1):5-10.
14. American Academy of Ophthalmology. *Preferred practice pattern diabetic retinopathy.* San Francisco: American Academy of Ophthalmology 1998.
15. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol.* 1994;118(4):445-50.
16. Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. *Arch Ophthalmol.* 1996;114(66-71).

- 1692 17. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid
1693 of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med.*
1694 1994;331(22):1480-7.
- 1695 18. Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo
1696 by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor
1697 chimeric proteins. *Proc Natl Acad Sci USA.* 1995;92(23):10457-61.
- 1698 19. Amano S, Rohan R, Kuroki M, Tolentino M, Adamis AP. Requirement for vascular
1699 endothelial growth factor in wound- and inflammation-related corneal
1700 neovascularization. *Invest Ophthalmol Vis Sci.* 1998;39(1):18-22.
- 1701 20. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971;285:1182-
1702 6.
- 1703 21. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal
1704 neovascularization with intravitreal anti-vascular endothelial growth factor antibody
1705 fragment. *Arch Ophthalmol.* 2002;120(3):338-46.
- 1706 22. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial
1707 growth factor is a secreted angiogenic mitogen. *Science.* 1989;246:1306-9.
- 1708 23. Malecaze F, Clamens S, Simorre-Pinatel V, et al. Detection of vascular endothelial
1709 growth factor messenger RNA and vascular endothelial growth factor-like activity in
1710 proliferative diabetic retinopathy. *Arch Ophthalmol.* 1994;112(11):1476-82.
- 1711 24. Schwesinger C, Yee C, Rohan RM, et al. Intrachoroidal neovascularization in transgenic
1712 mice overexpressing vascular endothelial growth factor in the retinal pigment epithelium.
1713 *Am J Pathol.* 2001;158(3):1161-72.
- 1714 25. Tolentino MJ, McLeod DS, Taomoto M, Otsuji T, Adamis AP, Luttj GA. Vascular
1715 endothelial growth factor is sufficient to produce iris neovascularization and neovascular
1716 glaucoma in a nonhuman primate. *Arch Ophthalmol.* 1996;114:964-70.
- 1717 26. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative
1718 diabetic retinopathy complicated by vitreous hemorrhage. *Retina.* 2006;26(3):275-8.
- 1719 27. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of iris neovascularization after
1720 intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy.
1721 *Am J Ophthalmol.* 2006;142:155-8.
- 1722 28. Mason JO, 3rd, Nixon PA, White MF. Intravitreal injection of bevacizumab (Avastin) as
1723 adjunctive treatment of proliferative diabetic retinopathy. *Am J Ophthalmol.*
1724 2006;142(4):685-8.
- 1725 29. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the
1726 treatment of proliferative diabetic retinopathy. *Ophthalmology.* 2006;113(10):1695 e1-15.
- 1727 30. Isaacs TW, Barry C. Rapid resolution of severe disc new vessels in proliferative diabetic
1728 retinopathy following a single intravitreal injection of bevacizumab (Avastin). *Clin*
1729 *Experiment Ophthalmol.* 2006;34(8):802-3.
- 1730 31. Adamis AP, Altaweel M, Bressler NM, et al. Changes in retinal neovascularization after
1731 pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology.* 2006;113(1):23-8.
- 1732 32. Gonzalez VH, Giuliari GP, Banda RM, Guel DA. Intravitreal injection of pegaptanib
1733 sodium for proliferative diabetic retinopathy. *Br J Ophthalmol.* 2009;93(11):1474-8.
- 1734 33. Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards A, et al. A phase II
1735 randomized clinical trial of intravitreal bevacizumab for diabetic macular edema.
1736 *Ophthalmol.* 2007;114(10):1860-7.

- 1737 34. Nguyen QD, Shah SM, Heier JS, et al. Primary end point (six months) results of the
1738 ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology*.
1739 2009;116(11):2175-81 e1.
- 1740 35. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE Study Ranibizumab
1741 Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular
1742 Edema. *Ophthalmology*. 2011;118(4):615-25.
- 1743 36. The Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating
1744 ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic
1745 macular edema. *Ophthalmology*. 2010;117(6):1064-77 e35.
- 1746 37. Ranibizumab significantly more effective than standard of care in treating vision loss due
1747 to DME, a serious complication of diabetes. [http://www.novartis.com/newsroom/media-](http://www.novartis.com/newsroom/media-releases/en/2010/1418121.shtml)
1748 [releases/en/2010/1418121.shtml](http://www.novartis.com/newsroom/media-releases/en/2010/1418121.shtml). Accessed November 18, 2010.
- 1749 38. Phase III study of lucentis showed rapid vision improvements sustained for two years in
1750 patients with diabetic macular edema [http://www.gene.com/gene/news/press-](http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=13287)
1751 [releases/display.do?method=detail&id=13287](http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=13287). Accessed March 21, 2011.
- 1752 39. Second lucentis phase III study meets primary endpoint for improved vision in patients
1753 with diabetic macular edema (DME). [http://www.gene.com/gene/news/press-](http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=13327)
1754 [releases/display.do?method=detail&id=13327](http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=13327), Accessed April 4, 2011
- 1755 40. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing
1756 intravitreal triamcinolone acetate and focal/grid photocoagulation for diabetic macular
1757 edema. *Ophthalmology*. 2008;115(9):1447-9, 9 e1-10.
- 1758 41. Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N. Tolerability and efficacy of multiple
1759 escalating doses of ranibizumab (Lucentis) for neovascular age-related macular
1760 degeneration. *Ophthalmology*. 2006;113(4):623 e1.
- 1761 42. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related
1762 macular degeneration. *N Engl J Med*. 2006;355(14):1419-31.
- 1763 43. Boyer DS, Heier JS, Brown DM, Francom SF, Ianchulev T, Rubio RG. A Phase IIIb
1764 study to evaluate the safety of ranibizumab in subjects with neovascular age-related
1765 macular degeneration. *Ophthalmology*. 2009;116(9):1731-9.
- 1766 44. Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial
1767 infarction, bleeding, and stroke associated with therapies for age-related macular
1768 degeneration. *Arch Ophthalmol*. 2010;128(10):1273-9.
- 1769
1770