Diabetic Retinopathy Clinical Research Network

Evaluation of Vitrectomy for Diabetic Macular Edema Study

Version 1.3

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CHAPTER 1.
BACKGROUND AND SYNOPSIS

This study is one of a series of studies being conducted by the Diabetic Retinopathy Clinical Research Network.

1.1 Study Rationale

Diabetic retinopathy is a disorder of major public health importance, accounting for the majority of visual loss among working age Americans. Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that can produce loss of central vision. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) estimate that after 15 years of known diabetes, the prevalence of diabetic macular edema is approximately 20% in individuals with type 1 diabetes mellitus (DM), 25% in individuals with type 2 DM who are taking insulin, and 14% in individuals with type 2 DM who do not take insulin.[1] The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that moderate vision loss, defined as a doubling of the visual angle (e.g., 20/20 reduced to 20/40 or worse), can be reduced by 50% by focal laser photocoagulation according to ETDRS protocol.[2] Although several treatment modalities are currently under investigation, the only demonstrated means to reduce the risk of vision loss from diabetic macular edema are ETDRS laser photocoagulation, as demonstrated by the ETDRS, and intensive glycemic control, as demonstrated by the Diabetes Control and Complications Trial (DCCT)[3] and the United Kingdom Prospective Diabetes Study (UKPDS).[4] In the DCCT, intensive glucose control reduced the risk of onset of diabetic macular edema by 23% compared with conventional treatment. Long-term follow-up of study subjects in the DCCT show a sustained effect of intensive glucose control, with a 58% risk reduction in the development of diabetic macular edema for the DCCT study subjects followed in the Epidemiology of Diabetes Interventions and Complications Study.[5]

The vitreous, which is a jellylike fluid that occupies about two-thirds of the volume of the eye, is thought potentially to play a role in the development of DME through mechanical mechanisms and/or physiologic mechanisms that lead to increased retinal vascular permeability. Vitrectomy has been used in the management of diabetic macular edema (DME) for many years. In many cases, this surgical procedure is performed because of macular traction and abnormality of the posterior hyaloid. In some cases, the procedure has been performed as a ‘last-resort’ measure in the judgment of an ophthalmologist when the eye has been nonresponsive to laser photocoagulation and other modalities. Despite the fact that thousands of eyes are estimated to have had vitrectomy for DME, there are limited available data on which to judge the merits and risks of the procedure for DME. The literature consists mainly of retrospective case series. The literature is reviewed in a separate document.

1.1.1 Theoretical Basis for Vitrectomy for DME

There are at least two avenues of investigation that support the theoretical value of vitrectomy for the treatment of DME, based on (1) vitrectomy for the relief of traction on the macula and (2) vitrectomy to improve oxygenation of the macula leading to decreased permeability with subsequent resolution or decrease in DME.

Vitrectomy to relieve biomechanical traction on the macula has been reported widely. Schepens and coworkers discussed the role of the vitreous and vitreomacular traction in cystoid macular edema in 1984.[6] Nasrallah et al observed in 1988 the resolution of diabetic macular edema in individuals with spontaneous separation of the vitreous gel from the retina.[7] In 1992, Lewis and coworkers reported success with vitrectomy and peeling of a “thickened hyaloid membrane” in eyes with DME that had this anatomical feature.[8] Since this report of a nonrandomized retrospective

case series, other authors have prospectively analyzed their series and supported the concept that relief of clear-cut anteroposterior traction, usually in the setting of an epiretinal membrane complex and associated vitreous adherence, may ameliorate macular thickening and edema in DME.[9-23] Evaluation of these individuals and documentation of pre and postoperative characteristics have been rendered vastly more objective by ocular coherence tomography and the Retina Thickness Analyzer. [16, 17, 19, 21-24] Series using OCT to image cases where vitreomacular traction is observed and in some cases treated, has confirmed the clinical impression of mechanical forces at work on the posterior retina and has documented the anatomic improvement with surgery.[16, 17, 19, 21-25] How and in which cases OCT could refine our ability to diagnose and define clinically important anatomical features or relationships has not been investigated. As Kaiser and coworkers have documented, the OCT findings in the cases that have thus far come to vitrectomy in these situations support a conclusion that the disease process has progressed very far and in many cases the individuals have actual traction retinal detachments in their maculae.[24] These severe cases are the exception in the spectrum of DME: most cases of macular edema have no obvious vitreomacular traction, but this factor has not been investigated adequately with our newer and more sophisticated imaging techniques. It is possible that subclinical traction on the macula exists in a large number of individuals with diabetes, whose internal limiting membranes at the vitreomacular interface often have a thickened, hypercellular appearance and whose vitreous gels, gradually contracting over many years, may exert subclinical but significant traction on the compromised diabetic macular vascular bed.

The other line of reasoning and prior research that supports the possibility that vitrectomy would help DME is that articulated by Steffanson and others indicating that posterior segment oxygenation improves after vitrectomy. [26, 27] Using oxygen sensors on the retinal surface, these investigators have shown that retinal oxygen tensions increase after the vitreous gel is removed and the posterior segment becomes perfused by relatively oxygen-rich aqueous humor. Supporting this conclusion is the additional observation that retinal vessels decrease in caliber after vitrectomy, presumably in response to the improvement in hypoxia, although confounding factors that could contribute to this decrease, such as the addition of endolaser retinal photocoagulation, have not been ruled out. Numerous lines of investigation have elucidated factors producing permeability in retinal blood vessels. One of the most central of these factors is Vascular Endothelial Growth factor (VEGF), formerly known as Vascular Permeability Factor (VPF).[28] VEGF is known to be upregulated by hypoxia, and downregulated by increased oxygenation. The speculated sequence of events in which vitrectomy produces improved oxygenation of the posterior segment, leading to downregulation of VEGF, leading to decreased vasopermeability, resulting in reduced macular thickening, is a plausible one. More rapid clearing of growth factors in the vitrectomized eye has also been postulated as a potential mechanism for this response.

1.2 Study Design

The study is designed as a prospective cohort study. A randomized trial design was considered but rejected after deciding that (1) there was insufficient equipoise on the part of the investigator group to randomize eyes with DME and vitreal traction to surgery or no surgery (thus eyes which potentially may benefit most from vitrectomy would not be included), and (2) there was insufficient information available on the natural course or surgical outcomes of eyes with DME but without significant traction.

A cohort study provides the opportunity to collect data prospectively using a standardized protocol to assess the potential benefits and risks of vitrectomy. The results can be used to determine whether proceeding with a randomized trial has merit and what the design of the trial should be. If

a randomized trial is to be conducted, the results plus the cohort study experience can be used to help design the RCT protocol.

1.3 Study Objectives

1. To provide information on the following outcomes in eyes with DME that undergo vitrectomy: visual acuity, retinal thickening, resolution of traction (if present), surgical complications.
2. To identify subgroups in which there appears to be a benefit of vitrectomy and subgroups in which vitrectomy does not appear to be beneficial.
3. To obtain data that can be used to plan a randomized trial.

1.4 Synopsis of Study Design

A. Major Eligibility Criteria

- Age >=18 years old
- At least one eye meeting all of the following criteria:
  - Vitrectomy being performed as treatment of DME.
  - Diabetic macular edema on clinical exam
  - Best corrected visual acuity 20/800 or better (E-ETDRS visual acuity score >= 3 letters)
    - Acuity in primary analysis cohort 20/63 to 20/400-see below)

B. Intervention

Vitrectomy performed by the investigator's usual routine.

C. Duration of Follow-Up: Three years

D. Follow-up Visit Schedule

Study visits for data collection at 3 and 6 months then 1, 2, and 3 years. Additional visits follow investigator's usual routine.

E. Main Outcomes

- Visual acuity
- Retinal thickening (measured on OCT)
- Surgical complications (including intraoperative and perioperative medical complications)

The 6-month data will be considered primary for efficacy analyses, since additional treatment beyond that time point may complicate interpretation of the results. Longer term follow-up will be necessary for documentation of complications, such as cataracts.

F. Sample Size:

Approximately 400 patients

- Approximately 200 patients meeting the following criteria: vitreomacular traction on OCT, visual acuity 20/63 to 20/400, retinal thickness >300 microns in the central subfield on OCT, and cataract extraction not performed in conjunction with vitrectomy.
- Approximately 200 additional patients undergoing vitrectomy for DME but not meeting the above criteria.

G. Schedule of Study Visits and Examination Procedures

	Study Month					
	0	**3**	**6**	**12**	**24**	**36**
E-ETDRS visual acuity[a]	x	x	x	x	x	x
Fundus photos	7F		7F	7F	7F	7F
OCT	x	x	x	x	x	x
IOP	x	x	x	x	x	x
Eye Exam[b]	x	x	x	x	x	x
Blood pressure	x			x	x	x
HbA1c[c]	x			x	x	x
Fluor. Angio[d]	x					

All procedures should be performed on the study eye only.

a=includes protocol refraction. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.

b=includes lens assessment using standard photos

c=does not need to be repeated if HbA1c and lab normal values are available from within the prior 3 months (at baseline, can be performed within 3 weeks after enrollment)

d=does not need to be performed if not part of usual care.

CHAPTER 2.
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Identifying Eligible Subjects and Obtaining Informed Consent

A minimum of 400 patients are expected to be enrolled with a goal to enroll an appropriate representation of minorities. Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. For subjects who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the patient by a study investigator and clinic coordinator. The patient will be given the Informed Consent Form to read. Patients will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study. Patients will be provided with a copy of the signed Informed Consent Form.

2.2 Eligibility Criteria

2.2.1 Subject-level Criteria

Inclusion

To be eligible, the following inclusion criteria (1-3) must be met:

1. Age >= 18 years
   - *Patients < 18 years old are not being included because DME is so rare in this age group that the diagnosis of DME may be questionable.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes*
     - *Current regular use of oral antihyperglycemia agents for the treatment of diabetes*
     - *Documented diabetes by ADA and/or WHO criteria (see Site Coordinator Manual)*
3. Able and willing to provide informed consent.

Exclusion

A patient is not eligible if any of the following exclusion criteria (4-6) are present:

4. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure and glycemic control).
   - *Patients in poor glycemic control who, within the last 4 months, initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next 4 months should not be enrolled.*
5. Patient is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the first year of the study.
6. Blood pressure >180/110 (systolic above 180 **OR** diastolic above 110).
   - *If blood pressure is brought below 180/110 by antihypertensive treatment, patient can become eligible.*

2.2.2 Study Eye Criteria

To be a study eye, all of the inclusion criteria (a-e) and none of the exclusion criteria (f-m) listed below must be met. A patient can have only one study eye. If both eyes are eligible and undergoing vitrectomy, the first eye having surgery will be the study eye.

The eligibility criteria for a study eye are as follows:

Inclusion

a. Vitrectomy being performed as treatment for DME.

b. E-ETDRS visual acuity 20/800 or better (E-ETDRS visual acuity score >= 3 letters).
   - Acuity in primary analysis cohort 20/63 to 20/400 as defined in section 7.1)

c. Definite retinal thickening due to diabetic macular edema based on clinical exam involving the center of the macula.
   - Central retinal thickness in primary analysis cohort > 300 microns on OCT as defined in section 7.1

d. Presence of vitreomacular traction associated with macular edema OR edema is felt to be too diffuse to respond to focal or grid laser OR edema judged to be inadequately responsive to previous treatment(s) and unlikely to benefit from further focal photocoagulation.

e. Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

Exclusion

f. Macular edema is considered to be due to a cause other than diabetic macular edema.
   - *For example, an eye should not be considered eligible if the macular edema is considered to be primarily related to cataract extraction.*

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

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

i. History of retinal macular photocoagulation, intravitreal corticosteroids, or other treatment for DME within 3.5 months prior to enrollment.
   - ***Note:*** *Patients are not required to have had prior macular photocoagulation to be enrolled.*

j. History of peripheral scatter photocoagulation within 4 months prior to enrollment or anticipated need within the 4 months following enrollment.

k. History of prior pars plana vitrectomy.

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

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

2.3 Screening Evaluation and Baseline Testing

2.3.1 Historical Information

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

2.3.2 Testing Procedures

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

If a procedure has been performed (using the study technique and by study certified personnel) as part of usual care, it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.

The testing procedures are detailed in the DRCR.net Testing Procedures Manuals. Visual acuity testing, ocular exam, fundus photography and OCT will be performed by certified personnel.

Testing will be performed on the study eye.

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in the study eye *(completion within 8 days prior to surgery is preferred, however, testing within 21 days of surgery is acceptable).*
   - If surgery is scheduled such that visual acuity will have been measured more than 8 days prior to surgery, when feasible the visual acuity should be remeasured within 8 days of surgery.
   - *This testing procedure has been validated against 4-meter ETDRS chart testing.*
2. OCT *(OCT3 or later version; done within 21 days prior to surgery).*
3. Ocular examination on study eye, including slit lamp, IOP measurement, lens assessment, and dilated fundus examination (including assessment of posterior hyaloid status and assessment of whether vitreomacular traction is present) *(done within 21 days prior to surgery).*
4. ETDRS protocol 7-standard field stereoscopic fundus photography (fields 1M, 2, 3M, 4, 5, 6, 7, reflex) *(done within 21 days prior to surgery).*
5. ETDRS fluorescein angiography (if performed as part of usual care).

Additional Testing will include:

6. Measurement of blood pressure.
7. HbA1c blood test.
   - *Does not need to be repeated if available in the prior 3 months. If not available at the time of surgery, the patient may be enrolled but the test must be obtained within 21 days after surgery.*

The fundus photographs, OCT, and fluorescein angiogram (if performed) will be sent to the Fundus Photograph Reading Center for grading, but patient eligibility is determined by the site (i.e., patients deemed eligible by the investigator will be enrolled without need for Reading Center confirmation).

CHAPTER 3.
VITRECTOMY

3.1 Introduction

While the vitrectomy itself is not part of the experimental design, investigators are encouraged to perform the vitrectomy in a standardized fashion as outlined below. The outlined procedure is consistent with the usual practices of vitreoretinal surgeons.

3.2 Pre-operative Care

Pre-operative care will be according to the investigator's usual routine.

3.3 Surgical Procedure

A standard pars plana vitrectomy will be performed by the investigator's usual routine. The procedure typically includes:

- Conjunctival incisions.
- Three pars plana sclerotomies, 3-4 mm posterior to the surgical limbus.
- Removal of the vitreous gel with peeling of the posterior hyaloid, if a posterior vitreous detachment is not initially present, and removal of peripheral vitreous leaving only a small residual vitreous skirt. Removal of residual posterior hyaloid if a posterior vitreous detachment is initially present.
- Engagement of visually significant epiretinal membranes and peeling them off the surface of the macula.
- Examination with the indirect ophthalmoscope and treatment of any peripheral breaks with laser or cryotherapy.
- Closure of the sclerotomies with absorbable suture and re-approximation of the edges of the conjunctival incisions.

Optional additional procedures at the discretion of the investigator:

- Removal of the internal limiting membrane.
- Use of agents to improve visualization of membranes, such as triamcinolone acetonide or indycyanine green dye.
- Use of corticosteroids (intravitreal, subtenon's, subconjunctival, oral, intravenous) at the close of the procedure.
- Use of endolaser.
- Cataract extraction.
- Use of 25 gauge vitrectomy system.

3.4 Postoperative Care

Postoperative care will be performed according to the investigator's usual routine.

Intravitreal and periocular steroids may be given in the first post-op week, but then should not be given thereafter until completion of the 6-month visit.

3.5 Cancellation of Surgery

If surgery is cancelled and never performed, the patient will not be continued in the study.

CHAPTER 4.
FOLLOW-UP VISIT SCHEDULE AND PROCEDURES

4.1 Follow-up Visit Schedule

The surgery date is considered to be study day 0. Study visits will be conducted at:

- 3 months ± 4 weeks
- 6 months ± 4 weeks
- 1 year ± 4 weeks
- 2 years ± 26 weeks
- 3 years ± 26 weeks

Note: A visit is not considered missed until the window for the next visit opens (out of window visits will be included in analysis).

Additional visits, including the initial post-op visits, will be conducted according to the investigator's usual routine and the patient's condition. The information collected at these visits will be summarized at the next protocol-specified visit.

4.2 Follow-up Visit Testing and Procedures

At each visit, an interval history will be elicited, which will include medical and surgical treatment of the study eye. Following the vitrectomy surgery, data will be collected from the patient chart on the vitrectomy procedure and intraoperative and postoperative complications.

The following procedures are performed at each protocol visit unless otherwise specified. The procedures are detailed in the DRCR.net Testing Procedures Manuals. Visual acuity testing, fundus photography, OCT, and ocular exam will be performed by certified personnel.

The following testing is done in the study eye at each protocol visit:

1. ETDRS protocol refraction and E-ETDRS visual acuity testing .
2. Ocular examination on study eye, including slit lamp, IOP measurement, and dilated fundus examination (including assessment of posterior hyaloid status and assessment of whether vitreomacular traction is present).
3. Cataract assessment with standard photographs.
4. OCT
   - Must be performed using the same OCT machine version and software used at baseline (e.g., OCT3 used throughout the study for a particular patient).
5. Stereoscopic fundus photography
   - ETDRS 7-fields (1M, 2, 3M, 4, 5, 6, 7, reflex) at 6 months and at yearly visits.

The following testing is done at the annual visits:

1. Measurement of blood pressure
   - Measured in sitting position after patient has been sitting for at least 5 minutes.
2. HbA1c
   - If an HbA1c test result is available from the prior 3 months, it does not need to be repeated at this visit.

The fundus photographs and OCTs will be sent to the Reading Center for grading.

CHAPTER 5.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

5.1 Additional Treatment for DME

While additional treatments for DME are not part of the experimental design, investigators are encouraged to follow a standardized approach to such treatments as follows:

First Six Months

Treatment decisions are at investigator discretion based on the patient's condition and the investigator's usual practice. The following are guidelines for management:

- During the first post-op week, intravitreal or peribulbar corticosteroids may be given, since the surgery is being performed under the assumption that structural, rather than vessel pathophysiology, is accounting for the edema. Thereafter, injectable corticosteroids should not be given prior to completion of the 6-month visit.
- Topical corticosteroids may be prescribed at the investigator's discretion.
- Laser and other treatments for DME generally should not be given until completion of the 6-month visit, although panretinal photocoagulation should be given promptly for study eyes developing high-risk PDR, eyes approaching high-risk PDR, and eyes developing rubeosis iridis during follow-up.

After First Six Months

Therapies for DME may be given at the discretion of the investigator. This includes treatment that might be received as part of another research study (see section 5.5).

5.2 Focal/Grid Laser Photocoagulation

If focal/grid macular photocoagulation is performed during the course of the study (after the first six months), the DRCR.net laser photocoagulation procedure should be used. The photocoagulation treatment technique, as described below, is a modification of the ETDRS technique and is the treatment approach that is commonly used in clinical practice and is the standard for all DRCR.net trials. The treatment 'session' may be completed fully at the initial 'sitting,' or it may be divided into multiple sittings at the investigator's discretion.

Note: Focal/grid macular photocoagulation (modified ETDRS protocol) should not be performed within the first 6 months.

A fluorescein angiogram may be used to guide the treatment at the investigator's discretion; if performed, it will not be sent to the Reading Center (fluorescein angiograms performed at baseline will be sent to the Reading Center).

Burn Characteristic	Focal / Grid Photocoagulation (modified-ETDRS technique)
Area Considered for Treatment	500 to 3000 microns from the center of macula No burns are placed within 500 microns of optic disk
Wavelength:	Green to yellow wavelengths
Burn Size	50 microns
Burn Duration	0.05 to 0.1 sec
Grid Treatment	If fluorescein angiography is performed: apply to all areas of diffuse leakage or nonperfusion within the area outlined above as well as to all areas with retinal thickening within the area outlined above If fluorescein angiography is not performed: apply to all areas with retinal thickening within the area outlined above
Burn Intensity	Barely visible (light grey)
Burn Separation	2 visible burn widths apart
Focally Treat Leaking MA	All leaking microaneurysms are focally treated, but only in areas of retinal thickening located within treatment area outlined above
Change MA Color	Not required, but at least a mild burn should be evident beneath all MAs

MA = microaneurysm

Note:

- *The investigator may choose any laser wavelength for photocoagulation within the green to yellow spectrum. The wavelength used will be recorded and any re-treatment should use the same wavelength.*
- *Lenses used for the laser treatment cannot increase or reduce the burn size by more than 10%.*

5.3 Panretinal Photocoagulation

PRP can be given if it is indicated in the judgment of the investigator. In general, PRP should not be given if the patient has less than severe NPDR. In general, PRP should be given promptly for previously untreated eyes exhibiting PDR with high-risk characteristics and can be considered for persons with non high-risk PDR or severe NPDR.

Burn Characteristics

Size (on retina)	500 microns
Exposure	0.1 seconds recommended, 0.05 to 0.2 allowed
Intensity	mild white
Distribution	edges 1 burn width apart
No. of Sessions/Sittings	unrestricted (each session generally should be completed in <6 sittings)
Nasal proximity to disk	No closer than 500 microns
Temp. proximity to center	No closer than 3000 microns
Superior/inferior limit	No further posterior than 1 burn within the temporal arcades
Extent	Arcades (~3000 microns from the macular center) to at least the equator
Min # of Final Burns:	1200
Wavelength	Green or yellow *(red can be used if vitreous hemorrhage is present precluding use of green or yellow)*

5.4 Diabetes Management

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

5.5 Participation in Other Studies Prior to the End of Three-year Follow-up

The Steering Committee may decide (with concurrence of the Data and Safety Monitoring Committee) to permit patients to participate in a new DRCR.net or other study after the first 6 months of this study. If the patient enters another research study, data will still be collected concurrently for this current study.

5.6 Patient Withdrawal and Losses to Follow-up

A patient has the right to withdraw from the study at any time. If a patient is considering withdrawing from the study, the Principal Investigator should personally speak to the patient about the reasons and every effort should be made to accommodate the patient. The Coordinating Center should be contacted prior to formally withdrawing the patient from the study. Ownership of the data collected up until the time of withdrawal is retained by the DRCR Network.

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

Patients who withdraw will be asked to have a final close-out visit at which the testing described for the outcome examination visits will be performed. Patients who have an adverse effect attributable

to a study treatment or procedure will be asked to continue in follow-up until the adverse event has resolved or stabilized, if not resolved or stabilized at the time of the final study visit.

Subjects who are determined to be ineligible or for whom there are substantial deviations from the protocol may be discontinued from the study.

Subjects who withdraw will not be replaced.

5.7 Discontinuation of Study

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

5.8 Contact Information Provided to the Coordinating Center

The Coordinating Center will be provided with contact information for each subject. Permission to obtain such information will be included in the Informed Consent Form. The contact information will be maintained in a secure database and will be maintained separately from the study data.

Phone contact from the Coordinating Center will be made with each patient in the first month after enrollment. Additional phone contacts from the Coordinating Center will be made, if necessary, to facilitate the scheduling of the patient for follow-up visits. A patient newsletter will be sent at least twice a year. A study logo item valued under $10 may be sent once a year.

Patients will be provided with a summary of the study results in a newsletter format after completion of the study by all patients. Patients may also be briefed about the results by the local center at a study visit or by telephone.

5.9 Patient Reimbursement

The study will be paying $25 per completed visit for the three follow-up visits in year 1 and one follow-up visit in each of years 2 and 3. Payment will not be made for missed visits. Payment will be made from the Coordinating Center following each visit. If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses.

5.10 General Considerations

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

The DRCRnet Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, Photography and OCT Testing Procedures Manual, and Site Procedures Manual) provide details of the examination procedures.

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

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

CHAPTER 6.
ADVERSE EVENTS

6.1 Events to be Reported

Surgical complications and other untoward events will be recorded on the follow-up exam forms and not on separate adverse event forms since the vitrectomy procedure is not considered part of the experimental design.

6.2 Reporting Requirements for Adverse Events

Each Principal Investigator is responsible for abiding by reporting requirements specific to his/her IRB.

6.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Committee will approve the protocol prior to its initiation and will review accrued data at intervals.

6.4 Risks and Discomforts

The vitrectomy is considered to be part of usual care and not part of an experimental protocol. In addition, all examination procedures are considered part of usual care although the procedures have been standardized for consistency across centers.

Patients will sign an institutional consent form for the surgery, which will list the risks and discomforts involved in the surgery. This is separate from the informed consent process for participation in the study. **There are no known risks or discomforts involved in participation in the study, which involves systematically collecting information in a prospective fashion.**

The sections below summarize the risks and discomforts that may be involved in the usual care of the patient during the period of time of prospective data collection.

6.4.1 Vitrectomy

6.4.1.1 Anesthesia

Anesthesia may be general endotracheal or local retrobulbar/peribulbar, usually with systemic sedation. Risks of systemic sedation and general anesthesia include cardiac arrhythmia and death. The risks of retrobulbar/peribulbar anesthesia include: retrobulbar hemorrhage; perforation of the eye by the needle; damage to the optic nerve; double vision lasting up to 24 hours or more; drooping of the eye lid lasting up to 24 hours or more; difficulty speaking or breathing; lightheadedness/syncope/vasovagal response; allergy to any components of the injection; life threatening response due to the spread of anesthesia to the brain stem, resulting in epileptic fits, drowsiness, confusion, loss of verbalization, convulsions, respiratory arrest, or cardiac arrest.

6.4.1.2 Surgical Procedure

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

6.4.2 Examination Procedures

The procedures in this study are part of daily ophthalmologic practice in the United States and pose no additional known risks. Dilating eye drops will be used as part of each exam.

6.4.3 Fundus Photography

Fundus photography carries no risk, although the camera flash may cause temporary discomfort for the patient.

6.4.4 Fluorescein Angiography

A fluorescein angiogram may be performed prior to surgery as part of usual care. In the procedure, a yellow dye is injected intravenously. Risks include but are not limited to: transient change in skin and urine color; nausea; allergic reaction to the dye; anaphylaxis and possible death (less than 1 in 100,000 people). The procedure will not be performed if medically contraindicated.

6.4.5 Optical Coherence Tomography

OCT carries no known risk. Dilating eye drops will be used as part of each exam.

CHAPTER 7.
STATISTICAL CONSIDERATIONS

7.1 Sample Size and Power Considerations

The sample size for the study has been projected to be 200 patients with a study eye meeting the following criteria (primary cohort):

- Vitreomacular traction on OCT
- Visual acuity 20/63 to 20/400
- Retinal thickness in the central subfield >300 microns on OCT
- Cataract extraction not performed in conjunction with vitrectomy

Additional patients undergoing vitrectomy for DME but not meeting the above criteria will be enrolled during the time period of enrollment of the primary cohort, up to a maximum of 200 patients.

This is a convenience sample based on the expected number of patients to be enrolled within 12 months. Enrollment is expected to average approximately 5 patients per year at each of 80 centers.

For dichotomous outcomes (e.g., worsening of visual acuity by 3 or more lines, improvement of visual acuity by 3 or more lines, resolution of edema), the table below shows the width of a 2-sided 95% confidence interval for various proportions for different sample sizes.

	Half-width of 2-sided 95% CI		
Expected Proportion	N=100	N=200	N=300
.5	.098	.069	.057
.4	.096	.068	.055
.3	.090	.064	.052
.2	.078	.055	.045
.1	.059	.042	.034

7.2 Analysis Plan

The analysis plan will be detailed in a separate document. It is summarized below.

7.2.1 Efficacy Analyses

Results will be tabulated separately for eyes in the primary cohort and those in the secondary cohort for the following:

- Proportion that experience an improvement in visual acuity
- Proportion that experience a worsening in visual acuity
- Distribution of the change in visual acuity
- Time course of changes in visual acuity
- Proportion that experience resolution of DME

- Proportion that experience resolution of traction (e.g., absence of vitreomacular interface abnormality)
- Proportion that experience at least a 50% reduction in retinal thickening
- Time course of changes in retinal thickening

Analyses will be conducted to try to identify factors associated with a favorable acuity and OCT outcome and factors associated with a poor outcome. Factors to be assessed will include the following:

- Definite presence of vitreomacular traction/interface abnormalities
- Prior focal laser photocoagulation vs. no prior laser
- Baseline visual acuity
- Prior cataract surgery
- Amount of retinal thickening
- Baseline level of retinopathy
- Use of intraocular steroids or other routes of administration
- Use of optional additional procedures at the discretion of the investigator (e.g., ILM removal, cataract extraction, or endolaser)
- Duration of diabetes
- HbA1c

Exploratory analyses will compare the results in this study with those of unoperated eyes in other DRCR.net studies matched for macular edema and, if possible, on degree of traction.

Analysis will be conducted at several time points. The primary analysis will be at 6 months. Additional analyses will be conducted after 1 year and after 3 years.

7.2.2 Safety Analyses

Data will be tabulated on the following:

- Surgical complications
- Development of retinal detachment and retinal tears
- Development of additional vitreomacular interface abnormalities
- Development or progression of cataract
- Occurrence of additional surgical procedures - cataract surgery, laser treatments, retinal detachment surgery, repeat vitrectomy, glaucoma surgery

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