Diabetic Retinopathy Clinical Research Network

An Observational Study in Individuals with Diabetic Retinopathy without Center-Involved DME Undergoing Cataract Surgery

(Protocol Q)

Version 1.0

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CHAPTER 1.
BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background and Rationale

1.1.1. Diabetes and Cataract

The presence of diabetes increases the probability of development of a cataract. Approximately 25% of patients with type 2 diabetes 30 years of age and older will undergo cataract surgery during a 10 year period.[1] Additionally, type 1 diabetic patients are also subject to increased rates of cataract surgery relative to age matched controls without diabetes.[2]

With more than 1.5 million cataract operations performed in people in the United States each year, of whom at least 15% have diabetes based on the prevalence of diabetes in this age group, any resulting vision loss from development of macular edema or exacerbation of pre-existing macular edema (post-surgical, diabetic, or both) will have an impact on many people annually. Despite the common occurrence of cataract surgery in individuals with diabetes, there are limited meaningful data regarding visual acuity outcomes and the incidence of development or progression of macular edema after surgery, including eyes with or without macular edema at the time of surgery. In some reports, cases with and without diabetic macular edema (DME) at the time of surgery are combined, which limits the interpretation of the results.[3-14]

1.1.2. Progression of Level of Diabetic Retinopathy after Cataract Surgery

Prior to the advent of phacoemulsification, cataract surgery with ICCE or ECCE had been reported to be a risk factor for the progression of retinopathy in patients with diabetes.[13, 15-17] Cataract surgery with phacoemulcification was expected to reduce the risk compared with the ICCE or ECCE due to smaller incision size and shorter surgery time and therefore reduced inflammation. Some reports suggest more frequent progression of the level of diabetic retinopathy (with or without macular edema) in eyes with phacoemulcification than would be expected if compared with similar eyes without the surgery, [18-21] while other reports do not find such a difference.[22-24] The reported rate of post-operative progression of DR has ranged from 12% to 56%.[16, 18, 19, 23-28] However, the increased risk of progression following phacoemulcification, beyond the progression rate which would be expected in the absence of cataract surgery, remains imprecise.

1.1.3. Diabetic Macular Edema vs Post-Surgical Cystoid Macular Edema

Part of the difficulty in understanding the impact of cataract surgery on macular edema stems from the fact that both DME (either due to, or independent of, cataract surgery) and a different type of macular edema, herein termed "post-surgical cystoid macular edema," can develop after cataract surgery. The pathophysiology of DME is characterized by manifestations of both retinal ischemia and increased retinal vascular permeability. DME results from abnormal leakage of macromolecules, such as lipoproteins, from retinal capillaries into the extravascular space followed by an oncotic influx of water into the extravascular space.[4] Abnormalities in the retinal pigment epithelium may also cause or contribute to diabetic macular edema. These abnormalities may allow increased fluid from the choriocapillaries to enter the retina or they may decrease the normal efflux of fluid from the retina to the choriocapillaris.[4] The mechanism of breakdown of the blood retina barrier at the level of the retinal capillaries and the retinal pigment epithelium may be due to changes in tight junction proteins such as occludin.[3] The presence and

severity of DME may be overlooked or underestimated in the setting of substantial cataract, shedding doubt on whether pre-existing DME is adequately managed prior to cataract surgery or whether the "development" of DME after cataract surgery is progression vs better visualization of pre-existing edema or both. In addition, some eyes with known DME may not receive adequate focal/grid photocoagulation (the current standard treatment for DME) due to decreased penetration of the laser light through the cataractous lens.

Independent of DME, post-surgical cystoid macular edema (CME) can develop following cataract surgery in people with or without diabetes.[9] Post-surgical CME is characterized on biomicroscopy as cystoid macular edema in the absence of microaneurysms or lipid. Typically, fluorescein angiography reveals parafoveal dilation of pre-existing capillaries (telangiectasis) and fluroescein leakage which culminates in a petaloid pattern of fluorescein surrounding the fovea in late phase frames, frequently accompanied by leakage of the optic nerve and sometimes additional cystoid accumulation of fluorescein outside of the macula. This macular edema may be driven by inflammation as it is frequently responsive to anti-inflammatory interventions, either corticosteroids or non-steroidal anti-inflammatory drugs or both. [5-8] Additionally, post-surgical CME shares features with the macular edema seen in phakic eyes with uveitis, and severe cases of post-surgical CME have shown chronic inflammatory cells within uveal tissue on post-mortem examination. Post-surgical CME frequently is managed with topical non-steroidal anti-inflammatory drugs,[5-7] although topical corticosteroid drops also have been recommended typically in conjunction with topical non-steroidal anti-inflammatory drugs. When the initial response to topical therapy does not appear adequate, many ophthalmologists use periocular or intravitreal steroids to manage post-operative CME.[11, 12, 14] Individuals with diabetes undergoing cataract surgery can develop post-surgical CME just as individuals without diabetes can develop this relatively common post-surgical complication. A recently conducted prospective study evaluating post-surgical CME on fluorescein angiography after uncomplicated phacoemulsification in individuals without diabetes reported an incidence of 9.1%; the rate of post-surgical CME that affects visual acuity is thought to be substantially lower, between 0 and 2%.[10]

1.1.4. Macular Edema After Cataract Surgery

Reports have suggested that macular edema (either post-surgical, diabetic, or both) after cataract surgery can be a frequent and complex problem, [13, 26-32] but the reports suggest that the incidence may be predominantly in patients with pre-existing diabetic retinopathy and pre-existing central macular thickening.[27, 33] The mechanism of the development or worsening of macular edema that occurs after cataract surgery has been debated. Some argue that macular edema progression in a person with diabetes represents an increased incidence or severity of post-surgical CME in eyes that already have aberrant hyperpermeable macular capillaries from pre-existing clinical or subclinical diabetic disease; others argue that the progression of edema is simply a worsening of pre-existing DME without a post-surgical mechanism. Finally, many believe a combination of these factors may contribute to progression of macular edema in a diabetic person following cataract surgery.

Regardless of whether DME progresses more often compared with the expected rate of progression if cataract surgery had not been done, macular edema (ME), either DME, or post-surgical CME, or both, appears to develop post-operatively more frequently than one would expect in the absence of cataract surgery. In a prior DRCR.net study evaluating intravitreal triamcinolone compared with focal/grid photocoagulation for treatment of DME, there were 32

eyes that had cataract surgery in which no intravitreal corticosteroid or anti-VEGF treatment was given within 4 months prior to the cataract surgery through the first post-cataract extraction visit and in which the pre-operative central subfield measurements were <250 microns. Mean visual acuity improved from 20/125 to 20/63; 32% of eyes had an increase ≥25 microns to ≥250 microns at approximately 4 months after cataract surgery among the 25 eyes with OCT data available at the 4 month post operative visit. It is unknown if the limited improvement was because of pre-existing macular damage or exacerbation of edema or both.

Flesner and coworkers evaluated 39 diabetic persons undergoing cataract surgery, half of whom had no diabetic retinopathy at the pre-operative exam. Four (10%) developed unilateral macular edema within 6 months of undergoing cataract surgery in their study eye relative to their control contralateral eye that did not undergo cataract surgery and two others developed macular edema in both eyes. Three of the 6 eyes that developed macular edema following cataract surgery lost visual acuity relative to pre-op levels. [26]

Kim and associates reported an incidence rate of 22% (95% confidence interval 13% to 35%) for macular edema following cataract surgery in 50 eyes, defined as an increase in OCT center point thickness of 30% relative to pre-surgery levels. [31] Only 3 eyes had pre-existing macular edema (defined as a central subfield thickness of 250 microns or greater, personal communication, Neil Bressler, September 25, 2008); so these results largely apply to patients without DME at the time of cataract surgery. DME was more likely to develop in eyes with at least moderate NPDR when compared with eyes with lesser degrees of DR, and increases in OCT thickness post cataract surgery were inversely related to visual acuity gains. Cataract did not limit the ability to obtain OCT measurement of macular edema prior to surgery. Unpublished data from Kim et al. from 17 eyes with pre-operative central subfield thickness less than 250 microns and some level of retinopathy shows 12% increased ≥25 microns to ≥250 microns at 3 months post operative.

1.1.5. Rationale for Observational Study in Patients with Diabetes Undergoing Cataract Surgery

In summary, despite the common occurrence of cataract surgery in individuals with diabetes, there are no large, prospective studies addressing the incidence of macular edema and visual acuity outcomes in this situation, and few studies describing the progression of the level of diabetic retinopathy after cataract surgery. Since cataract surgery in individuals with diabetes is so common and since limited data suggest the visual acuity outcome in those individuals is compromised whether they have pre-operative DME or not, the information to be obtained in the proposed study will have considerable clinical importance.

To address these issues in more detail, the objectives of this study in patients with diabetes undergoing phacoemulsification include the following: 1) document the frequency of post-operative macular edema as identified on OCT and subsequently imaged on fluorescein angiography (including post-surgical CME, post-surgical DME, or both types of ME, retina vascular leakage, and disc hyperfluorescence; 2) report visual outcomes of cataract surgery in this cohort and 3) document the progression of diabetic retinopathy.

Such information may be of value to determine if edema is noted frequently enough to warrant future clinical trials aimed at preventing this progression. This observational study also will determine the feasibility and logistics of interaction between cataract surgeon's office and DRCR

Network sites for randomized interventional trials in eyes with or without DME prior to cataract surgery.

1.2 Study Objectives

The objective of the study is to determine the incidence of progression to center-involved macular edema 16 weeks after cataract surgery in eyes with diabetic retinopathy and without definite center-involved DME. The incidence rates will be determined separately for each of the following subgroups:

1. Eyes in which no injection for DME was received recently prior to surgery or at the time of surgery*, each to be further stratified by whether or not there was a history of any other prior treatment for DME:
   a) No center involved DME and no non-center involved DME (i.e. no DME)
      - *(central subfield [CSF]<190 for women or CSF<210 for men, and all inner subfields [ISF]<260, and all outer subfields [OSF]<220)*
   b) No center involved DME and definite/uncertain non-center involved DME
      - *(CSF <190 for women or CSF<210 for men, and at least 1 ISF ≥260 or OSF≥220)*
   c) Uncertain center involved DME and no non-center involved DME
      - *(CSF 190 to 249 for women or CSF 210 to 249 for men, and all ISF <260, and all OSF<220)*
   d) Uncertain center involved DME and definite/uncertain non-center involved DME
      - *(CSF 190 to 249 for women or CSF 210 to 249 for men, and at least 1 ISF ≥260 or OSF≥220)*
2. Eyes with an injection for DME received recently prior to surgery or at the time of surgery*, stratified by whether the treatment was corticosteroids or anti-VEGF therapy.

* Intravitreal or peribulbar corticosteroids within the last 4 months prior to surgery or on the day of surgery; anti-VEGF therapy within the last 2 months prior to surgery or on the day of surgery.

1.3 Study Design and Synopsis of Protocol

A. Study Design

- Observational study

B. Major Eligibility Criteria

- Age >=18 years
- Type 1 or type 2 diabetes
- Only one study eye per subject may be enrolled. The study eye must meet the following:
  - Presence of cataract for which cataract surgery is scheduled
  - Presence of microaneurysms or at least mild non-proliferative diabetic retinopathy (level 20 or higher) on clinical exam
  - No presence of center-involved DME as evidenced by Zeiss Stratus OCT central subfield thickness <250 microns(or spectral domain OCT equivalent)
  - Visual acuity light perception or better.

C. Sample Size

Recruitment is planned for a period of up to 24 months. Distribution of enrolled eyes in the predefined subgroups as listed in section 7.1 will be evaluated after 6 months and a determination will be made at that time whether to continue or stop enrollment.

A maximum of 100 eyes in each of the subgroups with no center involved DME and no non-center involved DME (group 1a; with/without prior treatment for DME) will be enrolled. Once this goal is met, recruitment may be stopped in this subgroup. Overall, a maximum of 500 subjects will be enrolled with no restriction on the number per site.

D. Cataract Surgery

The cataract surgery itself is not part of the experimental design. The cataract surgery, including pre-operative and post-operative assessments and management should be by the usual manner of each cataract surgeon. The surgical notes and post-op records (specifically the operative report including medications used and any surgical complication, as well as post-operative exams) will be obtained by the clinical site through a record release requested by the subject.

E. Treatment

All treatment is at the discretion of the cataract surgeon and the investigator. Information will be collected on the treatments received pre-operatively, peri-operatively, and post-operatively for DME or CME (topical drops, laser, corticosteroids, anti-VEGF drugs, oral medications, vitrectomy, or others).

F. Follow-up Schedule

- Follow-up visits will occur at 4 weeks and 16 weeks ***following cataract surgery***.
- The first time any treatment for DME or CME other than topical drops is to be given, an additional visit will be completed at which OCT and fluorescein angiography will be performed prior to administering treatment.
- Additional visits to occur as needed based on usual care.

G. Main Efficacy Outcome

The following will be evaluated at the 16 week time point.

Primary outcome:

Within each of the subgroups of eyes with no center involved DME and no non-center involved DME (group 1a; with/without prior treatment for DME), the following will be evaluated:

a. Proportion of eyes that progressed to definite center involved edema, defined as meeting any of the following criteria:
   (1) OCT central subfield thickness ≥250 microns at 16 weeks and increased at least 1 log unit from baseline to 16 weeks
   (2) Increased at least 2 log units from baseline to 16 weeks
   (3) Any treatment for DME or CME other than topical drops was received after surgery, and criterion (1) or (2) was met prior to starting treatment
b. Of the eyes that did not progress to definite center involved edema above, proportion of eyes that progressed to definite non-center involved edema, defined as meeting any of the following criteria:
   (1) At least 1 ISF ≥310 microns at 16 weeks and the maximum corresponding ISF increased at least 1 log unit from baseline to 16 weeks OR at least 1 OSF ≥290 microns at 16 weeks and the maximum corresponding ISF increased at least 1 log unit from baseline to 16 weeks

(2) At least 1 ISF increased at least 2 log OCT units from baseline to 16 weeks OR at least 1 OSF increased at least 2 log units from baseline to 16 weeks
(3) Any treatment for DME or CME other than topical drops was received after surgery, and criterion (1) or (2) was met prior to starting treatment

c. Proportion of eyes that progressed to at least definite non-center involved edema (i.e., met either definition above).

Within each of the other subgroups of eyes, the following will be evaluated:

a. Proportion of eyes that progressed to definite center involved edema, defined as meeting any of the following criteria:
(1) OCT central subfield thickness ≥250 microns at 16 weeks and increased at least 1 log unit from baseline to 16 weeks
(2) Increased at least 2 log units from baseline to 16 weeks
(3) Any treatment for DME or CME other than topical drops was received after surgery, and criterion (1) or (2) was met prior to starting treatment

Secondary analyses on primary outcome: Evaluate potential baseline factors associated with the primary outcome (including central subfield thickness, HbA1c, cataract surgery in fellow eye, visual acuity, and retinopathy severity on clinical assessment)

Secondary outcomes to be evaluated in each subgroup:

- Visual acuity
- OCT measured central subfield thickness
- Presence of DME/CME/Combination on FAs (graded by Reading Center)
- Progression of diabetic retinopathy on clinical exam

H. Schedule of Study Visits and Examination Procedures

	Enrollment	0	4w±1w	16w±2w
Cataract Surgery		X		
E-ETDRS best corrected VA[a]	X		X	X
OCT[b]	X		X	X
Fluorescein angiography[c]				X
Eye Exam[d]	X		X	X
HbA1c[e]	X			

A medical history will be elicited at enrollment and an updated history at each visit. a= both eyes at each visit; includes protocol refraction in study eye at each follow-up visit and in both eyes at enrollment.
b=study eye only; also obtained prior to the first non-topical DME treatment
c= obtained prior to the fist non-topical DME treatment or at 16w if central subfield thickness ≥250μ and treatment for DME (other than topical treatment) has not already been given.
d= study eye only at baseline and follow-up visits.
e=does not need to be repeated if HbA1c and lab normal values are available from within the prior 12 weeks and can be performed within 3 weeks after enrollment.

1.4 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 DRCR.net Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, OCT Testing Procedures Manual, Digital Fluorescein Angiography Procedure Manual, Study Procedures Manual, and photography procedure manuals) 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 subjects to be enrolled by a site.

CHAPTER 2.
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Identifying Eligible Subjects and Obtaining Informed Consent

Subjects undergoing cataract surgery in an eye without center involved diabetic macular edema on OCT will be enrolled for a period of at least 6 months up to a maximum of 500 subjects, with a goal to enroll an appropriate representation of minorities. Distribution of enrolled eyes in predefined subgroups will be evaluated and a determination will be made after 6 months whether to continue or stop enrollment. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be enrolled up until the end date.

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 subject by a study investigator and clinic coordinator. The subject will be given the Informed Consent Form to read. Subjects will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study.

2.2 Subject Eligibility Criteria

2.2.1 Subject-level Criteria

Inclusion

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

1. Age >= 18 years
   - *Subjects <18 years old are not being included because cataract is so rare in this age group.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes*
     - *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes*
     - *Documented diabetes by ADA and/or WHO criteria (see Procedures Manual for definitions)*
3. At least one eye meets the study eye criteria listed in section 2.2.2.
4. Able and willing to provide informed consent.
5. Able and willing to provide a medical record release for cataract surgery data.

Exclusion

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

1. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control).
    - *Subjects 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.*
2. Subject is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the 16 weeks of the study.

2.2.2 Study Eye Criteria

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

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

Inclusion

To be eligible, the following inclusion criteria for the study eye must be met:

1. Presence of cataract for which cataract surgery is scheduled.
2. Presence of microaneurysms or at least mild non-proliferative diabetic retinopathy (level 20 or higher) on clinical exam.
3. Visual acuity light perception or better.
4. Zeiss Stratus OCT central subfield thickness <250 microns (or spectral domain OCT equivalent)

Exclusions

The following exclusions apply to the study eye only:

1. An ocular condition, other than cataract and diabetic macular edema, is present such that, in the opinion of the investigator, visual acuity might be affected now (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, nonretinal condition, epiretinal membrane or vitreo-macular traction) or during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.).
2. History of major ocular surgery (including vitrectomy, scleral buckle, any intraocular surgery, etc.) within prior 4 months or major ocular surgery other than cataract anticipated within the next 4 months following enrollment.

2.3 Screening Evaluation and Baseline Testing

2.3.1 Historical Information

A history will be elicited from the subject 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, as well as ocular diseases, surgeries, and treatment.

2.3.2 Baseline Testing Procedures

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

- If a procedure has been performed (using the study technique and by study certified personnel) as part of usual care, it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.
- The testing procedures are detailed in the DRCR.net Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, OCT Testing Procedures Manual, Digital Fluorescein Angiography Procedures Manual, Study Procedures Manual, and photography procedure manuals). Visual acuity testing, ocular exam, and OCT will be performed by DRCR.net certified personnel.
- Maximum time windows from the completion of each procedure to the day of surgery have been established.

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in each eye. *(within 28 days prior to surgery)*
    - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[34]
    - *If the E-ETDRS visual acuity letter score is 0, then counting fingers, hand motion, and light perception are assessed.*
2. OCT on the study eye *(within 28 days prior to surgery)*
    - OCTs may only be graded by the reading center if determined likely to need manual grading
3. Ocular examination on the study eye including slit lamp and dilated fundus examination. *(within 28 days prior to surgery)*
4. Laboratory Testing- HbA1c
    - *HbA1c does not need to be repeated if available in the prior 3 months. If not available at the time of enrollment, the subject may be enrolled but the test must be obtained within 3 weeks after enrollment.*

2.4 Enrollment of Eligible Subjects

Prior to enrollment, the following should be confirmed:

1. The subject's understanding of the study and commitment to the follow-up schedule.
2. The subject is scheduled for cataract surgery, and the surgery date is within 28 days after the baseline assessments.

CHAPTER 3. CATARACT SURGERY

3.1 Introduction

The cataract surgery itself is not part of the experimental design. As such, cataract surgeons will not be considered investigators for this protocol and surgical centers will not be involved with the research.

3.2 Surgical Procedure

The cataract surgery, including pre-operative and post-operative assessments and management, should be by the usual manner of each cataract surgeon. The surgical notes and post-op records (specifically the operative report including medications used and any surgical complication, as well as post-operative exams) will be obtained by the clinical site through a record release requested by the subject.

3.3 Rescheduling or Cancellation of Surgery

If surgery is not completed on the scheduled date, the surgery should be rescheduled as soon as possible. If surgery is rescheduled more than 28 days after baseline assessments were completed, the baseline measurements should be reassessed prior to the new surgery date. If the subject is no longer eligible for the study on reassessment, he/she may be dropped.

CHAPTER 4. FOLLOW-UP VISITS AND TREATMENT

4.1 Visit Schedule

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

- 4±1 weeks and 16±2 weeks ***following cataract surgery***.
- Additional visits to occur as needed based on usual care.

All treatment is at the discretion of the cataract surgeon and the investigator. Information will be collected on the treatments received pre-operatively, peri-operatively, and post-operatively for DME or CME (topical drops, laser, corticosteroids, anti-VEGF drugs, oral medications, vitrectomy, or others).

The first time any treatment for DME or CME other than topical drops is to be given, an additional visit will be completed at which OCT and fluorescein angiography will be performed prior to administering treatment.

4.2 Testing Procedures

The following procedures will be performed at each protocol visit unless otherwise specified. All of the testing procedures do not need to be performed on the same day, provided that they are completed within the time window of a visit and prior to initiating any treatment.

Testing procedures at unscheduled visits are at investigator discretion. However, procedures that are performed should follow the standard DRCRnet protocol for each procedure.

1. E- ETDRS visual acuity testing in each eye (best corrected).
    - A protocol refraction in the study eye is required at all protocol visits. Refraction in the nonstudy eye is not required. When a refraction is not performed, i.e. at unscheduled visits, the most-recently performed refraction is used for the testing.
    - If the E-ETDRS visual acuity letter score is 0, then counting fingers, hand motion, and light perception are assessed.
2. OCT on the study eye
    - OCTs may only be graded by the reading center if determined likely to need manual grading
3. Ocular exam on study eye including slit lamp examination and dilated fundus examination.
4. Fluorescein angiography
    - Obtained at 16 week visit for all study eyes if OCT CSF ≥250 microns and treatment for DME (other than topical treatments) has not been given. If FA is to be obtained based on this criterion, the eye will be classified by the investigator as one of the following:
        (1) **CME Only:** Presence of post-surgical CME as defined below, without the presence of DME.
            Post-surgical CME is defined as the presence of ALL of the following:
            a. CSF >=250 microns on OCT

b. Disc hyperfluorescence by 5 minutes on investigator assessment of fluorescein angiography at the given follow-up visit
c. Accumulation of fluorescein in a cystoid pattern around the fovea for at least 3 contiguous clock hours on investigator assessment of fluorescein angiography at the given follow-up

(2) **DME Only:** Presence of DME, without the presence of *both* disc hyperfluorescence and accumulation of fluorescein in a cystoids pattern (as defined above in b and c).

(3) **CME+DME Combined-Mechanism:** Presence of both DME and post-surgical CME as defined above.

- FAs will be graded by a reading center for classification of DME/CME/Combination/Indeterminate

CHAPTER 5.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

5.1 Complications of Cataract Surgery

Complications of cataract surgery are managed by the cataract surgeon as judged indicated.

5.2 Treatment of Macular Edema in Nonstudy Eye

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

5.3 Diabetes Management

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

5.4 Subject Withdrawal and Losses to Follow-up

A subject has the right to withdraw from the study at any time. If a subject is considering withdrawal from the study, the principal investigator should personally speak to the subject about the reasons, and every effort should be made to accommodate the subject.

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 subjects who cannot be contacted by the site. The Coordinating Center will be responsible for classifying a subject as lost to follow-up.

Subjects who withdraw will be asked to have a final closeout visit at which the testing described for the protocol visits will be performed.
Subjects who withdraw or are determined to have been ineligible post-enrollment may be replaced in the enrollment total.

5.5 Discontinuation of Study

The study may be discontinued by the Executive Committee prior to the preplanned completion of follow-up for all subjects.

5.6 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 may be maintained in a secure database and will be maintained separately from the study data.

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

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

5.7 Subject Reimbursement

The study will be paying the subject $25 per completed protocol visit to cover travel and other visit-related expenses. Payment will be made from the Coordinating Center. Additional travel expenses may be paid or reimbursed via gas cards for subjects with higher expenses.

610
611 **5.8 Medical Records**
612 Subjects will sign a record release to obtain operative and postoperative records from the cataract
613 surgeon's office.

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 cataract surgery 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 Risks

6.3.1 Risks of Cataract Surgery

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

Complications of the cataract surgery itself include the development of post-surgical cystoid macular edema 1% to 2% of the time in people with or without diabetes, transient or sustained increase in intraocular pressure which could lead to glaucoma or blindness, corneal edema from endothelial cell loss, iris abnormalities, loss of vitreous, retinal tear or detachment, posterior vitreous detachment, epiretinal membrane, ptosis, diplopia, decentration of IOL, opacity of capsule, retained cataract remnants.

6.3.2 Risks of Eye Examination and Tests

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. There is a rare risk of an allergic response to the topical medications used to anesthetize the eye or dilate the pupil. Dilating drops rarely could cause an acute angle closure glaucoma attack, but this is highly unlikely since the subjects in the study will have had their pupils dilated many times previously.

6.3.3 Fluorescein Angiography

In the fluorescein angiogram 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.

6.3.4 Optical Coherence Tomography

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

CHAPTER 7.
STATISTICAL METHODS

7.1 Overview

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

The primary objective of the study is to determine the incidence of progression to center-involved diabetic macular edema (DME) 16 weeks after cataract surgery in eyes with diabetic retinopathy and without definite center-involved DME. The incidence rates will be determined separately for each of the following subgroups:

1. Eyes in which no injection for DME was received recently prior to surgery or at the time of surgery*, each to be further stratified by whether or not there was a history of any other prior treatment for DME:
    a) No center involved DME and no non-center involved DME (i.e. no DME)
        - *(CSF <190 for women or CSF<210 for men, and all ISF <260, and all OSF<220)*
    b) No center involved DME and definite/uncertain non-center involved DME
        - *(CSF <190 for women or CSF<210 for men, and at least 1 ISF ≥260 or OSF≥220)*
    c) Uncertain center involved DME and no non-center involved DME
        - *(CSF 190 to 249 for women or CSF 210 to 249 for men, and all ISF <260, and all OSF<220)*
    d) Uncertain center involved DME and definite/uncertain non-center involved DME
        - *(CSF 190 to 249 for women or CSF 210 to 249 for men, and at least 1 ISF ≥260 or OSF≥220)*
2. Eyes with an injection for DME received recently prior to surgery or at the time of surgery*, stratified by whether the treatment was corticosteroids or anti-VEGF therapy.

    * Intravitreal or peribulbar corticosteroids within the last 4 months prior to surgery or on the day of surgery; anti-VEGF therapy within the last 2 months prior to surgery or on the day of surgery.

7.2 Sample Size

Recruitment is planned for a period of up to 24 months. Distribution of enrolled eyes in the predefined subgroups as listed in section 7.1 will be evaluated after 6 months and a determination will be made at that time whether to continue or stop enrollment.

A maximum of 100 eyes in the subgroup with no center involved DME and no non-center involved DME (group 1a; with/without prior treatment for DME) will be enrolled. Once this goal is met, recruitment may be stopped in this subgroup. Overall, a maximum of 500 subjects will be enrolled with no restriction on the number per site.

If the rate of progression is 5% in each of these groups (and if N=50 with prior treatment group and N=50 without prior treatment group), the half width of the confidence intervals would be around 6% with this sample size.

	Half-width of 2-sided 95% CI		
Proportion progressed to edema	**N=50**	**N=75**	**N=100**
0.05	0.06	0.05	0.04
0.10	0.08	0.07	0.06

7.3 Statistical Analysis Plan

7.3.1 Primary Outcome

7.3.1.1 Primary Analysis

As stated in section 7.1, the primary objective of the study is to determine the incidence of progression to center-involved diabetic macular edema (DME) 16 weeks after cataract surgery in eyes with diabetic retinopathy and without definite center-involved DME. The incidence rates at the 16 week time point will be determined separately for each of the predefined subgroups as listed in section 7.1. Progression to edema will be defined separately according to the predefined subgroup, as detailed below. Point estimates and 95% confidence intervals will be evaluated for each. Similar analyses will be conducted at the 4-week visit.

Within each of the subgroups of eyes with no center involved DME and no non-center involved DME (group 1a; one subgroup with prior treatment for DME and one subgroup without prior treatment for DME), the following will be evaluated:

a. Proportion of eyes that progressed to definite center involved edema, defined as meeting <u>any</u> of the following criteria:
   (1) OCT central subfield thickness ≥250 microns at 16 weeks and increased at least 1 log OCT unit from baseline to 16 weeks
   (2) Increased at least 2 log units from baseline to 16 weeks
   (3) Any treatment for DME or CME other than topical drops was received after surgery, and criterion (1) or (2) was met prior to starting treatment
b. Of the eyes that did not progress to definite center involved edema above, proportion of eyes that progressed to definite non-center involved edema, defined as meeting <u>any</u> of the following criteria:
   (1) At least 1 ISF ≥310 microns at 16 weeks and the maximum corresponding ISF increased at least 1 log unit from baseline to 16 weeks <u>OR</u> at least 1 OSF ≥290 microns at 16 weeks and the maximum corresponding ISF increased at least 1 log unit from baseline to 16 weeks
   (2) At least 1 ISF increased at least 2 log units from baseline to 16 weeks <u>OR</u> at least 1 OSF increased at least 2 log units from baseline to 16 weeks
   (3) Any treatment for DME or CME other than topical drops was received after surgery, and criterion (1) or (2) was met prior to starting treatment
c. Proportion of eyes that progressed to <u>at least</u> definite non-center involved edema (i.e., met either definition above).

Within each of the other subgroups of eyes, the following will be evaluated:

a. Proportion of eyes that progressed to definite center involved edema, defined as meeting any of the following criteria:
   (1) OCT central subfield thickness ≥250 microns at 16 weeks and increased at least 1 log unit from baseline to 16 weeks

(2) Increased at least 2 log units from baseline to 16 weeks
(3) Any treatment for DME or CME other than topical drops was received after surgery, and criterion (1) or (2) was met prior to starting treatment

7.3.1.2 Analysis of Type of Edema in Eyes that Progressed

For eyes with OCT central subfield ≥ 250 microns at 16 weeks, the type of edema to which the eye progressed will be evaluated based on the reading center grading of FAs. The distribution of the type of edema will be provided.

7.3.1.3 Factors Associated with Outcome

Potential factors associated with the primary outcome (other than the prespecified primary subgroups in section 7.1) will be evaluated in exploratory analyses to determine if there are any subgroups in which there appears to be more progression of edema at 16 weeks. Point estimates and 95% confidence intervals will be provided for these secondary subgroup analyses. Event rates in different subgroups will be compared using Fisher's Exact Test. The study is not expected to have sufficient statistical power for definitive conclusions in all subgroups.

The subgroups may include but are not limited to those tentatively described below. The definitions will be reassessed after completion of enrollment to determine if the distributions are sufficient for analysis:

- Baseline visual acuity: 69 letters or better, 54-68 letters, 39-53 letters, 38 letters or worse
- Prior PRP: yes/no
- Baseline severity of retinopathy based on clinician assessment: microaneurysms only, mild/moderate NPDR, severe NPDR, PDR
- History of cataract surgery in fellow eye: yes/no
- Baseline HbA1c: < 8%, >= 8%
- Age at enrollment: below median/above median
- Diabetes type: Type 1, Type 2, Uncertain
- Gender: male/female

7.3.2 Secondary Outcomes

The following secondary outcomes will be evaluated at 16 weeks in each subgroup defined in section 7.1. Point estimates and 95% confidence intervals will be provided.

- Visual acuity letter score >= 73 (Snellen equivalent approximately 20/40 or better)
- Visual acuity improvement of ≥10 letters from baseline
- Visual acuity loss of ≥10 letters from baseline
- Central subfield thickness measured by OCT
- Mean change in retinal thickness from baseline
- Progression of diabetic retinopathy

7.3.3 Clinician Assessment of CME

The percentage agreement of investigator classification of DME, CME, or combination with the reading center assessment will be calculated at the 16 week visit for eyes with OCT central subfield ≥ 250μ.

CHAPTER 8. REFERENCES

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