Diabetic Retinopathy Clinical Research Network

Subclinical Diabetic Macular Edema Study

Version 1.2

June 1, 2005

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CHAPTER 1.
BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background and Rationale

1.1.1 Macular Edema and Diabetic Retinopathy

The complications of diabetic retinopathy remain the most common cause of blindness among American adults 20-74 years of age,[2] with nearly 4% of individuals with type 1 diabetes meeting the definition of legal blindness[3] and many more suffering from moderate visual loss. Nearly 99% of type 1 diabetics develop diabetic retinopathy within 20 years of their initial diagnosis.[4]

The microvascular complications of diabetic retinopathy are due to elevated blood glucose levels[5] with selective loss of pericytes, thickening of the retinal capillary basement membrane, microaneurysm formation, and retinal capillary closure.[6] The most common cause of visual loss in diabetes is retinal macular edema, in which there is swelling (or thickening) of the central retina (or "macula") due to excessive permeability of the retinal blood vessels.[3] Indeed, a recent epidemiologic study estimates that more than 4 million Americans have diabetic retinopathy with at least 747,000 harboring vision-threatening macular edema.[7] Diabetic macular edema can be asymptomatic as suggested by relatively good visual acuities of some participants with edema in the National Eye Institute-sponsored Early Treatment Diabetic Retinopathy Study.[8] Therefore, routine screening examinations by eye care professionals are recommended at regular intervals.[9] When an eye care provider's clinical examination identifies retinal edema that involves or threatens the fovea (center of the macula), laser photocoagulation usually is recommended to reduce the risk of any additional visual acuity loss that is at least moderate (at least 3 lines of visual acuity loss or 15 letters assuming 5 letters per line of vision).[1] Other factors are also important including extent of retinal thickening, presence and location of hard exudate, level of visual acuity, and change since a previous visit in these factors. Once treated, individuals are monitored closely for the need for additional treatment and other complications of diabetic retinopathy.[9]

1.1.2 Current Diagnosis of Diabetic Macular Edema and the Potential of OCT

The clinical standard for the detection of retinal edema is to view the macula with a lens at the slit lamp through a pharmacologically dilated pupil. This is a subjective process that is highly dependent on observer skill and experience, study participant cooperation, the degree of pupillary dilation, the presence of media opacity (e.g., cataract), and the pattern and degree of retinal swelling. Several years ago, a medical device entered the market that can objectively measure retinal morphology called an Optical Coherence Tomography (OCT) scanner.[10-22] OCT is a noninvasive, non-contact, high resolution scan of the retina based on the light-reflecting properties of the layers of the retina. OCT creates a cross-sectional image of the retina with a resolution of 10 microns, enabling evaluation of the macular contour and retinal fluid collections. Given the tremendous public health impact of diabetic retinopathy, including diabetic macular edema, and the skill and equipment needed for biomicroscopic examination, DRCR.net investigators hypothesize that detection of macular edema by an objective instrument such as the OCT followed by prompt evaluation and treatment when necessary might improve visual acuity outcomes for many diabetic study participants. In the ETDRS, eyes with clinically significant macular edema without center involvement had a visual acuity loss of 3 or more lines in treated eyes at a rate of about 2% at 1 year and 5% at 2 years. It is unknown if this is the expected rate of visual loss in eyes with OCT center point thickness of 200 to 299 microns or if the rate in such eyes would be closer to the ETDRS visual loss rate for eyes with center involvement at 2 years (about 7 to 8%). It also is unknown how much OCT adds to periodic clinical examinations in the management of subclinical thickening in eyes with relatively good vision.

Currently, laser photocoagulation treatment is indicated when clinically significant macular edema is present. However, when macular edema is not apparent on clinical examination but OCT demonstrates mild central thickening (center point thickness 200 to 299 microns), standard practice is observation without treatment.

1.1.3 Preliminary Studies

At least two studies have shown that mild abnormal thickening on OCT may not correspond to edema recognized by biomicroscopy.[23, 34] A recently conducted masked non-randomized prospective clinical case series compared contact lens biomicroscopy with Optical Coherence Tomography (OCT) for the detection of diabetic macular edema, confirming the notion that retinal thickening detected by OCT might not be seen on contact lens examination of the fovea in subjects with diabetic retinopathy.[23] Study participants consisted of a convenient cohort of consecutive patients with diabetes seen at the Wilmer Eye Institute's Retina Division at the Johns Hopkins University School of Medicine. Exclusion criteria included the presence of any pathology, other than diabetes, that could affect retinal thickness or preclude identification of edema involving the center of the macula. Case characteristics were recorded and eyes were examined by one of four experienced retina specialists using contact lens biomicroscopy. The presence of edema involving the center of the macula ("macular edema") was assessed as definitely present, questionably present, or definitely not present. OCT testing was performed and interpreted by trained technicians, masked to the physicians' assessment of macular edema.

1.1.3.1 Characteristics of Participants in One Preliminary Study

Of 107 individuals asked to consider participation in a preliminary study in August and September of 2002, 97 (91%) agreed to participate, completed the informed consent process, and were enrolled, suggesting a high rate of participation for the proposed DRCR.net protocol on Subclinical Diabetic Macular Edema. Two study participants were excluded after enrollment because one was unable to complete OCT testing during the clinic visit due to time constraints and another left prior to OCT testing without offering an explanation, suggesting that most individuals eligible for the proposed protocol will be able to complete a screening OCT evaluation. One hundred seventy-two eyes of 95 study participants completed the study. OCT scans were of sufficient quality for interpretation in 170 (99%) of 172 cases, suggesting that most individuals screened for enrollment for this DRCR.net protocol will have adequate OCT scans. In both cases of insufficient scan quality, the OCT operator attributed poor image acquisition to media opacity. Case characteristics are summarized in Tables 1 and 2 below, suggesting that the inclusion criteria for the proposed DRCR.net protocol is representative of many individuals enrolled in the Preliminary Study at Johns Hopkins.

Table 1. Continuous Case Characteristics (N=172)

Characteristic	Minimum	Maximum	Mean ± Standard Deviation
Age (years)	30	94	62 ± 12
Duration of DM (years)	1	54	19 ± 11
# of Focal Treatments	0	9	1.5 ± 1.8
# of Scatter Treatments	0	8	0.8 ± 1.4
Visual Acuity (logMAR)	2.00(2/200)	-0.1(20/15)	0.33(20/43) ± 0.34(17 letters*)

* Approximately 3.4 lines assuming 5 letters per line.

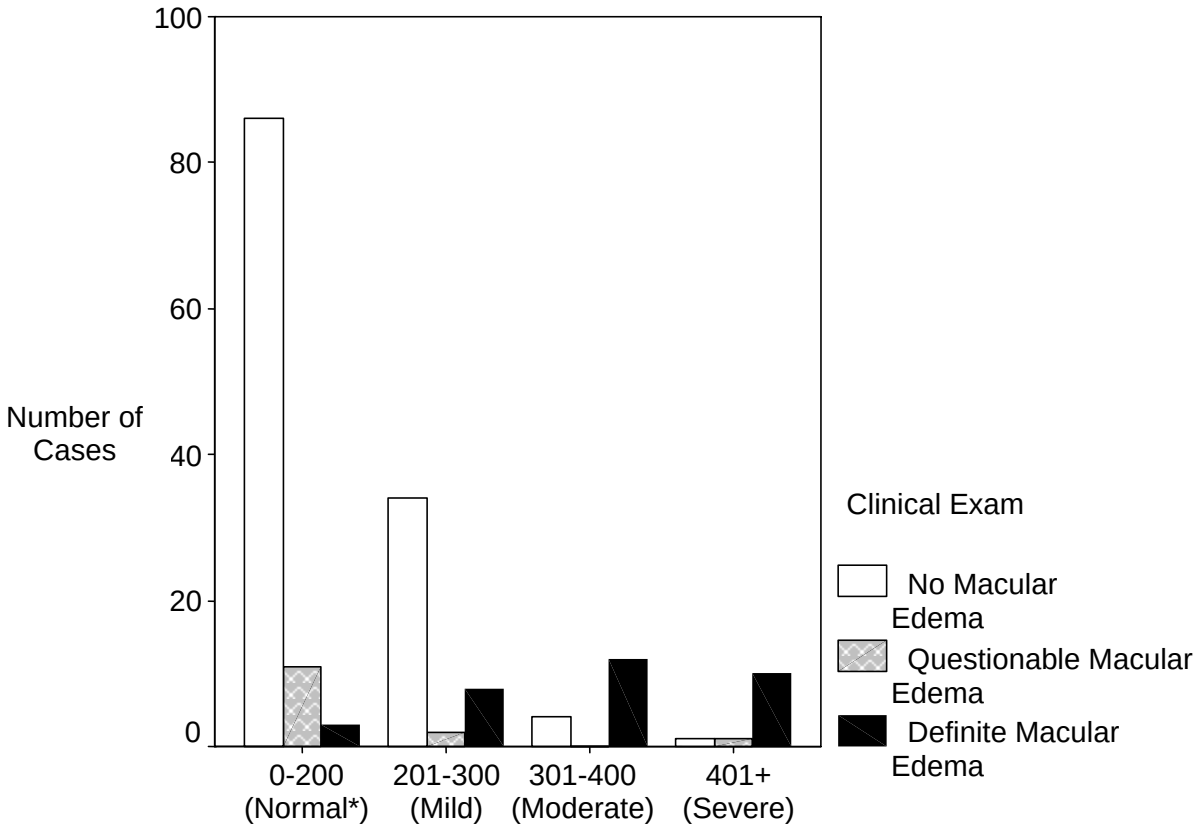
Table 2. Categorical Case Characteristics (N=172)

Characteristic	Number (Percent)
Race	
Caucasian	114 (66%)
African American	48 (28%)
Asian	5 (3%)
Other	5 (3%)
Gender	
Men	88 (51%)
Women	84 (49%)
Diabetes Type	
Type 1	35 (20%)
Type 2	137 (80%)
Lens Status	
Phakic	134 (78%)
Pseudophakic	38 (22%)
Level of Diabetic Retinopathy	
No Retinopathy	4 (2%)
Mild Nonproliferative	23 (13%)
Moderate Nonproliferative	43 (25%)
Severe Nonproliferative	33 (19%)
Proliferative	69 (40%)

1.1.3.2 OCT versus Clinical Exam Results in a Preliminary Study

Of the 172 eyes, edema involving the center of the macula by biomicroscopy was definitely present in 33 (19%), questionably present in 14 (8%), and definitely not present in 125 (73%) cases. Objective macular thickness measurements were obtained by OCT in all 14 cases with questionable macular edema by contact lens exam. The clinical assessment of macular thickening demonstrated good positive correlation with increasing OCT center point thickness (Pearson's coefficient = 0.63; P<.001).

Results organized by OCT thickness stratification are summarized in the figure below.



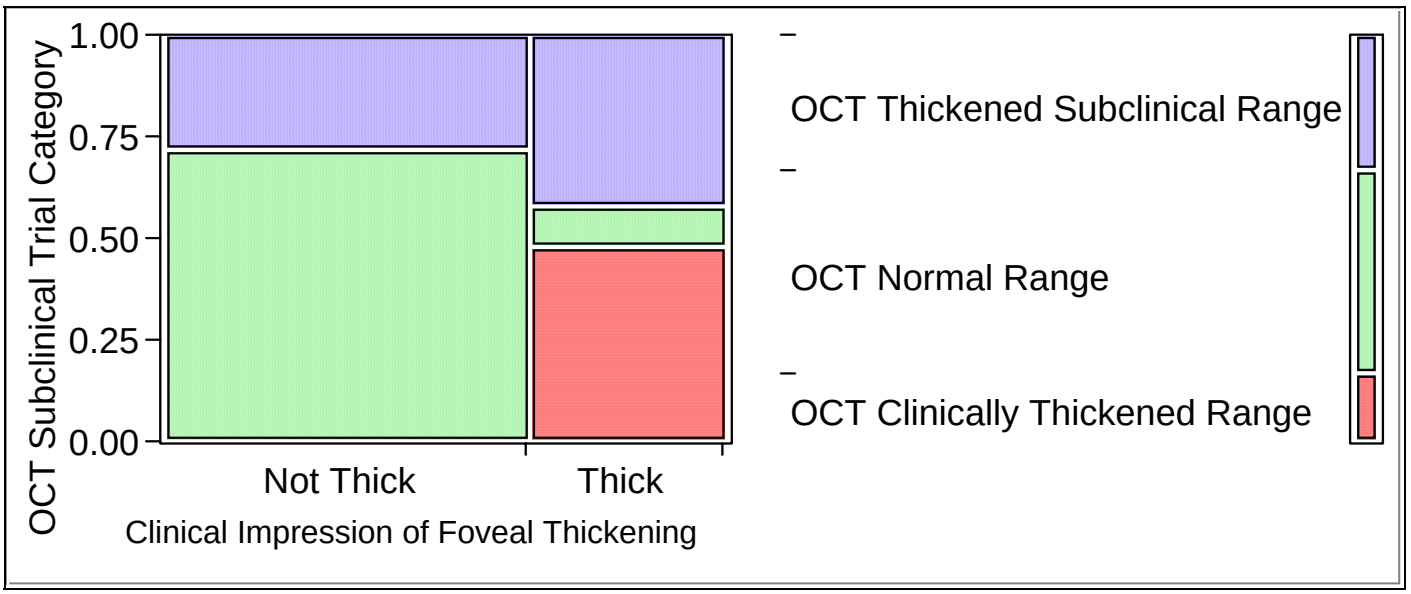
* OCT center point thickness less than or equal to 200 microns (considered no OCT thickening as determined from a large cohort of normal individuals).[11, 14, 16, 20-22]

Overall agreement between contact lens exam and OCT was only 119 (69%) of 172 (weighted kappa=.38; P<.001). However, the majority of disagreement occurred for cases with mild OCT thickening (greater than 200 microns but no greater than 300 microns) where agreement was only present in 10 (23%) of 44 eyes. When cases of mild thickening were excluded, overall agreement was good and improved to 109 (85%) of 128 (weighted kappa=.70; P<.001). Agreement between contact lens examination and OCT for the detection of diabetic macular edema was poor when OCT thickening was mild. These results are indirectly corroborated by several previous studies evaluating objective measurement techniques in diabetic macular edema[20-22, 25] and by a second prospective study using a 78D non-contact lens examination compared with the central subfield thickness.

1.1.3.3 OCT versus Clinical Examination Results in a Second Preliminary Study

Normative data from Browning[34] of 52 eyes, using OCT 3, indicate that the central subfield mean value is 197 microns +/- a standard deviation of 31 microns. Thus, if 250 microns to 350 microns is used as definite thickening of the central subfield on OCT, using a 78D indirect lens for biomicroscopy, among 47 eyes with this thickening on OCT, thickening of the macula was *not* detected on biomicroscopic examination in 26 eyes (55%) as shown in the figure below.

Mosaic Plot



Clinical Impression of Foveal Thickening by OCT Subclinical Trial Category

Count Total % Col % Row %	OCT Clinically Thickened Range	OCT Normal Range	OCT Thickened Subclinical Range	
Not Thick	0	67	26	93
	0.00	46.85	18.18	65.03
	0.00	93.06	55.32	
	0.00	72.04	27.96	
Thick	24	5	21	50
	16.78	3.50	14.69	34.97
	100.00	6.94	44.68	
	48.00	10.00	42.00	

These studies suggest that biomicroscopy is relatively insensitive for the detection of mild macular thickening apparent on OCT. The term “subclinical macular edema” is proposed to designate eyes with mild macular thickening by objective imaging methods since this thickening was not detected reliably by biomicroscopy. The short and long-term clinical significance of subclinical edema is unknown. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal laser photocoagulation reduces by 50% the risk of at least moderate vision loss in study participants with macular edema involving or threatening the center of vision.[1] It may not be reasonable to extrapolate ETDRS results to all cases of subclinical edema and apply focal laser photocoagulation to cases that do not appear thickened clinically because the ETDRS results for clinically significant macular edema likely may not have included many cases of subclinical macular edema.

1.1.4 Potential Public Health Impact of Subclinical Macular Edema Detected by OCT

If at least 25% of cases with no edema apparent on clinical examination have subclinical macular edema,[23, 34] subclinical macular edema may affect many patients in the United States with diabetes, and many more throughout the world. The goal of this DRCR.net protocol is to follow individuals with subclinical macular edema in order to understand the clinical significance (or insignificance) of this condition. The study would determine how often diabetic study participants

with subclinical macular edema (no clinically apparent macular edema by biomicroscopy but with center point thickening detected by OCT at baseline of at least 200 microns but less than or equal to 299 microns) progress to macular edema on OCT (at least 300 microns) which almost always is clinically apparent *and* increases 50 microns from baseline. The study would also determine the timing of this progression, the indicators of risk for this progression, and the frequency (as well as timing and indicators of risk) for application of focal laser photocoagulation or other treatment for diabetic macular edema prior to progression to clinically apparent macular edema. Analyses of the central subfield will be done in parallel.

This study is pertinent because if such individuals or subset of high risk individuals progress often to clinically apparent macular edema, or edema that results in application of focal photocoagulation, then the presence of subclinical macular edema or subclinical central subfield edema by periodic OCT testing of all patients with diabetes and no clinically apparent macular edema could serve as an important marker for eyes at higher risk of developing clinically apparent thickening. One then might consider monitoring these people more frequently to detect potential vision-threatening retinopathy earlier. In contrast, if few individuals with subclinical macular edema progress to clinically apparent macular edema within a couple of years, then periodic OCT testing for subclinical macular edema may not be necessary.

Furthermore, if a relatively benign therapy for macular edema existed, before visual acuity had been lost, one might consider testing that therapy in individuals with subclinical macular edema at high risk of progressing to clinically apparent macular edema. Information about the natural history of subclinical macular edema is necessary to determine the necessity and feasibility of future trials that would investigate the effectiveness of treating subclinical edema with laser photocoagulation or other interventions shown to be indicated for diabetic macular edema before the edema becomes clinically apparent. Such studies would be designed to determine if earlier intervention could reduce the risk of vision loss compared with continued observation until edema becomes clinically apparent.

Since OCT devices are now widely available in U.S. ophthalmic practices that specialize in the management of retinal problems,[24] the routine detection of subclinical macular edema by including OCT scanning in routine screening paradigms of individuals with diabetes is a possibility. The detection of retinal thickening at earlier stages using this technology could lead to the earlier treatment of vision-threatening complications of diabetic retinopathy and improve visual outcomes for many patients with diabetic retinopathy. However, further studies are necessary to confirm the importance of "subclinical" thickening detected by OCT, prompting this current protocol.

It is expected that most cases of subclinical macular edema in individuals with diabetes will be in those that have at least some retinopathy; furthermore, it is expected that individuals with subclinical macular edema who progress to at least 300 microns with at least a 50 micron increase will have some retinopathy at baseline. However, it is important to confirm these expectations in this study as well as to have information on the OCT-measured thickness of the retina in individuals with diabetes who do not have retinopathy.

1.2 Study Objectives

- Primary Objectives:
  - To determine how often study participants' eyes with subclinical diabetic macular edema (defined as no edema involving the center of the fovea as determined by biomicroscopy

but with center point thickness on OCT of at least 200 microns but less than or equal to 299 microns) progress over a 2-year period to edema on OCT of at least 300 microns (which is almost always clinically apparent) *and* increase at least 50 microns from baseline or are treated for diabetic macular edema among individuals with more than minimal retinopathy (greater than level 20).

- To determine mean OCT retinal thickness measurements and confidence intervals in subjects with diabetes and no or minimal non-proliferative diabetic retinopathy (level 20 or less).

- Secondary Objectives:
  - To explore whether subgroups of participants show any trend towards the presence of subclinical macular edema based on early stages of retinopathy, duration of diabetes and other baseline factors.
  - To determine indicators of risk for cases of subclinical diabetic macular edema that progress to center point thickness of 300 microns *and* increase at least 50 microns from baseline as well as the time of progression.
  - To determine timing and indicators of risk for application of laser photocoagulation or other treatment for diabetic macular edema *before* OCT thickness of at least 300 microns *and* increase of at least 50 microns from baseline have developed.
  - To determine the relationship between center point progression of edema on OCT and progression of edema on fundus photographs.

1.3 Study Design and Synopsis of Protocol

A. Study Design

- Prospective, multi-center observational study.
- The study consists of a baseline phase and follow-up phase.

B. Baseline Phase

1. Major Eligibility Criteria

- Age >=18 years.
- Study eye with best corrected E-ETDRS acuity >= 74 letters (20/32 or better).
  - Macular thickness on stereoscopic fundus examination judged to be normal and no treatment anticipated for edema threatening the macula. *Cases with no edema involving the center of the fovea but in which laser photocoagulation or other treatment for macular edema is judged indicated because of retinal thickening threatening the fovea on clinical examination will be excluded since the impact of treatment at baseline in those cases will make it difficult to determine the natural history of subclinical macular edema.*
- After enrollment of 100 individuals with no or minimal non-proliferative diabetic retinopathy (level 20 or better) in at least one eye, study eye eligibility will be restricted to include only eyes with at least mild non-proliferative diabetic retinopathy at level 35 or higher (worse), that is, microaneurysms plus at least one other feature of diabetic retinopathy such as a dot or blot hemorrhage, nerve fiber layer infarct, or lipid.

Study participants may have one or two study eyes at the time of study entry. However, if a participant is enrolled with only one study eye, the fellow eye cannot become a study eye during follow-up.

2. OCT Testing

OCT of the macula will be performed.

- If center point thickness is <200 or >=300, the eye is not eligible for the follow-up phase.
- If center point thickness is 200 to 299, the eye is eligible for the follow-up phase.

C. Follow-up Phase

1. Eligibility Criteria

To continue in the follow-up phase, the participant must have at least one eye with OCT center point thickness of 200 to 299 microns that meets the eligibility criteria listed in section 2.2.

2. Duration of Follow-Up: Two years, with exams after 1 year and 2 years.

E. Main Outcomes

Primary: OCT center point of at least 300 microns ***and*** an increase of at least 50 microns from baseline at 1-year or 2-year study visits, ***or*** treatment for diabetic macular edema.

F. Main Safety Outcomes

None.

G. Timing of Outcome Assessments

Primary outcome at 2 years (preliminary outcome assessment at 1 year; additional outcomes and indicators for risk described over time).

H. Sample Size

- 220 individuals with OCT center point thickness of at least 200 microns and less than or equal to 299 microns with no clinically apparent edema involving the center of the macula and no edema threatening the center of the macula.
- 100 participants with no diabetic retinopathy or microaneurysms consistent with level 20 in at least 1 eye.

I. Schedule of Study Visits and Examination Procedures

	Study Month				
Procedure	**0**	**6***	**12**	**18***	**24**
E-ETDRS visual acuity[a]	x		x		x
Fundus photos	7 fields		3 fields		3 fields
OCT of study eye	x		x		x
Eye Exam	x		x		x
Blood pressure	x		x		x
HbA1c[b]	x		x		x
Telephone Call[c]		x		x	
History of Rx for DME[d]			x		x

Testing is on both eyes at the initial visit except for OCT which is obtained only if both eyes appear to be eligible at the initial visit by clinical examination. Testing is only performed on the study eye at follow-up unless otherwise specified below.

a = at 0 months, pre-dilation visual acuity by routine clinic measurement of 20/50. If E-ETDRS by DRCR.net protocol not obtained pre-dilation, post-dilation E-ETDRS protocol visual acuity testing is performed. Post-dilation E-ETDRS visual acuity must be at least 30 minutes after any examination or imaging procedure. If E-ETDRS post-dilation is a letter score less than 74, then it must be repeated undilated at a later time and be at least a letter score of 74 to continue in the study. Also includes DRCR.net protocol refraction at 0, 12, and 24 months. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.[33] Visual acuity will be tested on both eyes at all visits.

b = 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).

c = telephone call to determine if any treatment for macular edema given in either eye and to reinforce need for follow-up

d = determined for both eyes at each visit.

Note: If a study eye is going to receive treatment for macular edema, the procedure listed above for the annual visits should be completed.

If a study subject receives treatment for edema in between protocol visits without obtaining an OCT, OCT will NOT be obtained at a later visit. Further follow-up in the study will not occur.

*Not associated with a patient visit.

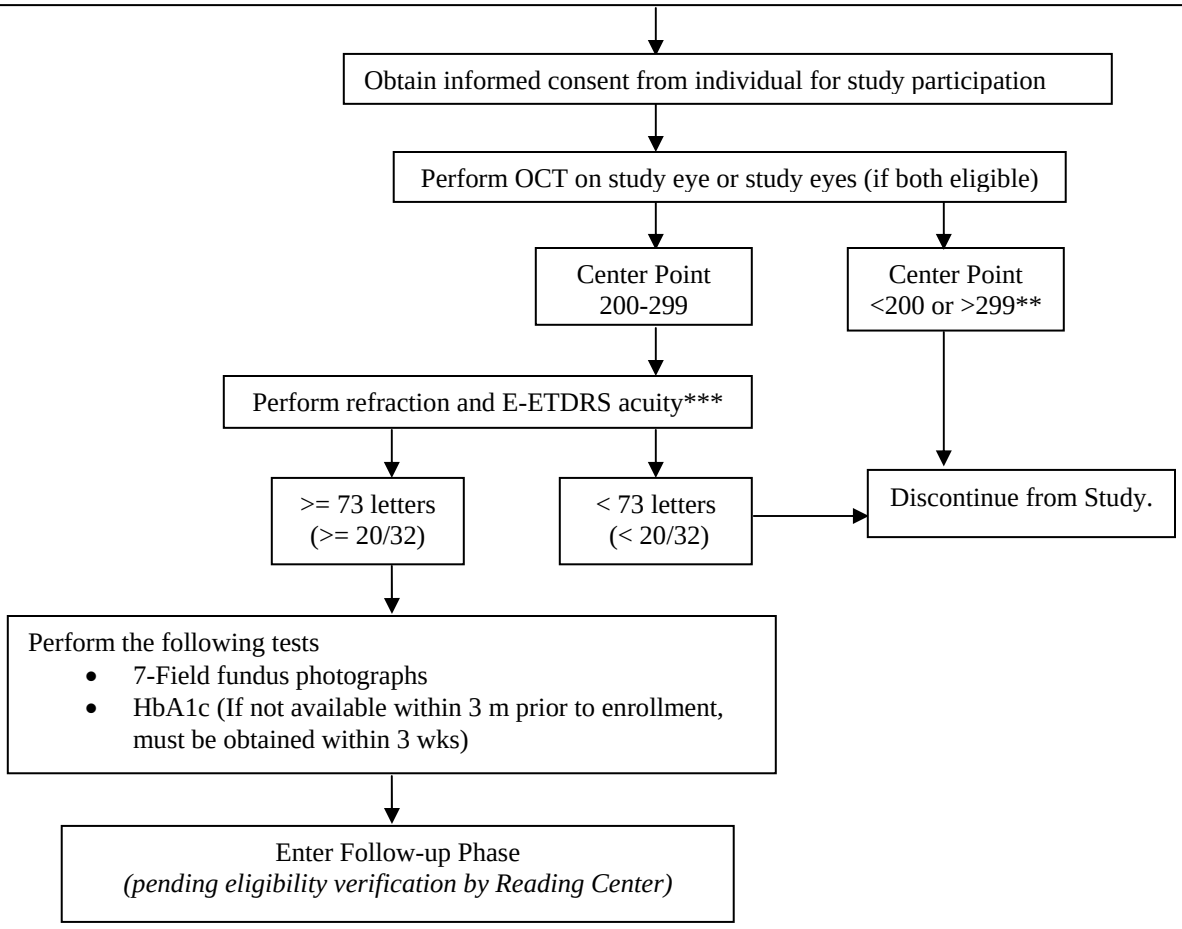
Baseline Phase Flow Chart

General Eligibility:

- >= 18 years old
- Diabetes (type 1 or type 2)
- No hx of chronic renal failure requiring dialysis or kidney transplant and no hx of pancreatic transplant
- No participation in an investigational ocular trial requiring follow up
- No medical treatment for the retina with medications that have been proven to affect edema.
- No hx of systemic corticosteroids within 4 m and no current use of topical, rectal, or inhaled corticosteroids more than 2x/wk
- Blood pressure <=180/110

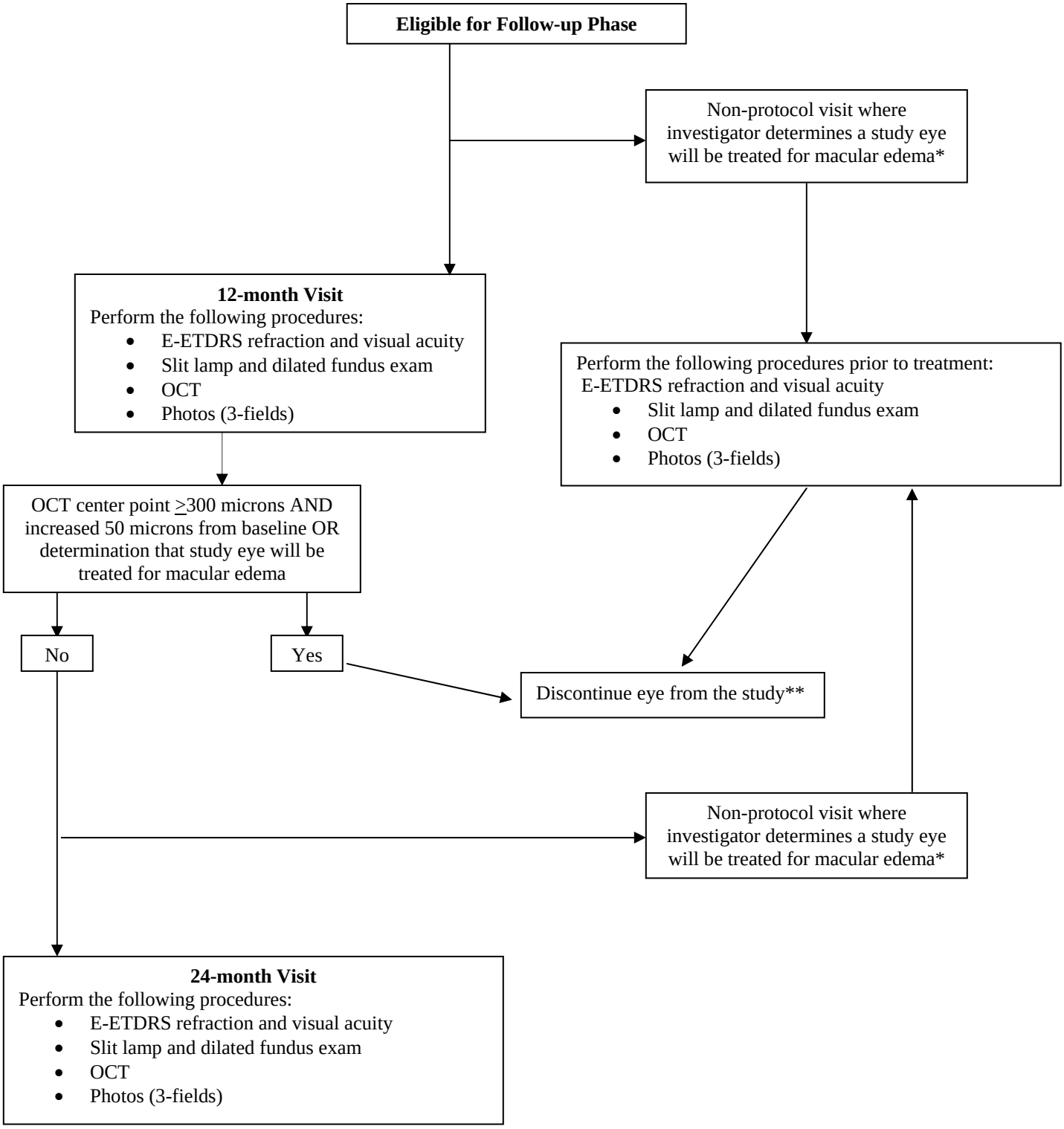
At least one eye with:

- No thickening of center point of macula based on clinical examination
- No prior treatment for DME
- Visual acuity >= 20/50 with office chart (or >=20/32 with E-ETDRS)
- Based on clinical exam, no retinal thickening threatening the fovea, such that treatment is indicated
- Mild nonproliferative diabetic retinopathy at level 35 or higher (worse) retinopathy *****
- No macular pathology other than diabetic retinopathy (DR)
- No ocular condition (other than diabetes) present that might affect macular edema or alter visual acuity during course of study
- No hx of PRP within 6 m, and no anticipated need within next 4 m
- No hx of major ocular surgery within prior 6 m, and none anticipated within next 4 m



* There will be no restriction on level of retinopathy until 100 subjects with no or minimal retinopathy in at least one eye are enrolled
** For the first 100 subjects with no retinopathy or level 20, E-ETDRS acuity testing and fundus photos obtained regardless of OCT thickness
*** Does not need to be repeated if performed as part of screening. If post-dilation acuity is worse than 20/32, acuity can be repeated within 8 days.

Follow-up Phase Flow Chart



* Can occur at any point during the two year study
** If subject has two study eyes, the subject may remain in the study as long as one eye has not been treated

1.4 General Considerations

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

The DRCR.net Procedures Manuals (Visual Acuity-Refraction Testing Procedures Manual, 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.

No site should enroll more than 20% of the sample size in order to include several investigators involved in the determination of clinically apparent edema.

CHAPTER 2.
BASELINE PHASE

2.1 Identifying Eligible Subjects and Obtaining Informed Consent

Individuals with diabetes who do not have apparent macular edema involving the center of the macula on clinical exam and who meet the eligibility criteria listed in section 2.2 are eligible to participate.

Recruitment will continue until 220 enrolled subjects have been found to be eligible for the follow-up phase (OCT center point thickness between 200 and 299 microns).

Initially, there will be no restriction of the level of retinopathy that is present for an eye to be eligible. After 100 subjects are enrolled with no diabetic retinopathy or only microaneurysms consistent with level 20 in a study eye, eligibility of an eye will require that retinopathy of level 35 or greater be present (to increase the likelihood that the eye will be eligible for the follow-up phase).

One goal is 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, including the baseline OCT, written informed consent will be obtained. For subjects who are considered potentially eligible for the study based on a routine-care exam (i.e., visual acuity by routine clinical procedures of 20/50 or better and no macular edema involving the center of the macula detected by biomicroscopic examination), the study protocol will be discussed with the potential study participant by the study investigator and clinic coordinator. The potential subject will be given the Informed Consent Form to read.

2.2 Study Subject Eligibility Criteria

2.2.1 Subject-level Criteria

Inclusion

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

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

Exclusion

A potential study participant is not eligible if any of the following exclusion criteria (5-12) are present:

5. History of chronic renal failure requiring dialysis or kidney transplant.
6. History of pancreatic transplant.
7. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure and glycemic control).
   - *Potential participants 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.*
8. Participation in an investigational ocular trial requiring follow-up at the time of study entry.
9. Any medical treatment for the retina or medication that has been proven to affect edema.
10. History of systemic (e.g., oral, IV, IM, epidural, bursal) corticosteroids within 4 months prior to enrollment or topical, rectal, or inhaled corticosteroids in current use more than 2 times per week.
11. Participant is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the 2 years of the study.
12. Blood pressure > 180/110 (systolic above 180 **OR** diastolic above 110).
    - *If blood pressure is brought below 180/110 by anti-hypertensive treatment, the subject can become eligible.*

2.2.2 Study Eye Criteria

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

A potential subject may have two study eyes only if both are eligible at the time of enrollment.

The eligibility criteria for a study eye are as follows:

Inclusion

a. Best corrected E-ETDRS visual acuity score of >= 74 letters (i.e., 20/32 or better).
   - *This testing procedure has been validated against 4-meter ETDRS chart testing.*[33]
     - *Clinic measurement using habitual correction should be 20/50 or better before dilation **and before protocol OCT is obtained** unless protocol E-ETDRS was obtained as part of routine care. In the latter situation, protocol E-ETDRS score must be >=74.*
     - *If subject is found to meet eligibility criteria based on fundus examination and protocol E-ETDRS was not obtained as part of routine care prior to dilation, then protocol E-ETDRS may be obtained after dilation to confirm visual acuity score of >=74.*
       - *If post-dilation protocol refraction and letter score is less than 74 when protocol E-ETDRS was not obtained as part of routine care prior to dilation, then the subject may return within 8 days after the fundus examination and be enrolled if pre-dilation E-ETDRS visual acuity letter score following protocol refraction is at least 74.*

b. No retinal thickening involving the center point of the macula due to diabetic retinopathy ***based on clinical examination***.

- *Assessment made **prior** to an evaluation of OCT data.*

c. An enrollment limit on subjects with no diabetic retinopathy or microaneurysms only (level 20) in at least 1 eye will be set at 100 patients. After this quota is met the following will also be required for inclusion into the study:

- Mild nonproliferative diabetic retinopathy at level 35 (that is, microaneurysms plus at least one other feature of diabetic retinopathy such as a dot or blot hemorrhage, nerve fiber layer infarct, or lipid) or higher level of (worse) retinopathy as determined by the investigator and verified by the Reading Center.

<u>Exclusion</u>

d. Retinal thickening due to diabetic retinopathy based on clinical examination involving the macula such that laser photocoagulation or other treatment is judged indicated within next 4 months.

- *Assessment made **prior** to an evaluation of OCT data.*

f. Macular pathology other than diabetic retinopathy, including vitreomacular interface abnormalities.

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

h. History of treatment for macular edema including focal/grid macular photocoagulation or corticosteroids.

i. History of panretinal scatter photocoagulation (PRP) within 6 months prior to enrollment.

j. Anticipated need for PRP in the 4 months following study entry.

k. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 6 months or anticipated within the next 4 months following enrollment.

2.2.3 Fellow Eye Criteria

In potential study subjects with only one eye meeting criteria to be a study eye at the time of enrollment, there are no exclusion criteria for the fellow eye.

2.3 Screening Evaluation and Baseline Testing

2.3.1 Historical Information

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

2.3.2 Testing Procedures

The following procedures are needed to assess eligibility or to serve as a baseline measure for the follow-up phase of the study or both.

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, Photography and OCT Testing Procedures Manual, and Site Procedures Manual). Visual acuity testing, ocular exam, fundus photography, and OCT must be performed by certified personnel.

In some cases, assessment of eligibility and the baseline OCT may require at least two visits although all testing can be done on the same day, including E-ETDRS visual acuity testing after dilation. Since all of the testing is not required to be on the same day, maximum time windows from the completion of each procedure to the day of enrollment have been established.

Testing will be performed on each eye unless otherwise specified.

1. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester, including protocol refraction *(done within 8 days of OCT).*

    - If the initial acuity was measured with an office chart and neither eye is found to be eligible for the follow-up phase on OCT, the E-ETDRS acuity measurement is not needed if the patient's study eye(s) has retinopathy level 35 or greater (worse).

2. Ocular examination on study eye, including slit lamp and dilated fundus examination *(done within 21 days prior to enrollment **but prior to OCT**).*

3. OCT *(done within 21 days prior to enrollment, **but after the ocular examination** on the study eye has detected no clinically apparent edema involving the fovea or requiring treatment because of edema threatening the fovea).*

    - The center point macular thickness will be determined from a fast macular scan. The technical component of the OCT costs will be paid for by the study. This measurement must be confirmed by the Reading Center in order for the subject to be eligible for the follow-up phase of the study.

    - All efforts will be made to reduce the chances of an ungradeable OCT scan. The OCT technicians will be instructed to aim for a signal strength of at least 6, and standard deviation of the center point <10% of the center point. However, if the technician determines the scan is acceptable with a signal strength less than 6 or standard deviation greater than 10%, it may be submitted. If an adequate scan cannot be obtained, the site should evaluate the size of the pupils and, if indicated, dilate the pupils again and then repeat the scan.

4. ETDRS protocol 7-standard field stereoscopic fundus photography (fields 1M, 2, 3M, 4, 5, 6, 7, reflex) *(done within 21 days prior to enrollment). The technical component of the photography costs will be paid for by the study.*

    - Photos will be obtained after the OCT is performed for all study eyes with no or minimal retinopathy and for those eyes eligible for the follow-up phase.

    - Photos do not need to be obtained for eyes with retinopathy level 35 or greater (worse) that are not eligible for the follow-up phase.

5. Measurement of blood pressure *(done within 21 days prior to enrollment).*

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

2.4 Subjects Not Eligible for the Follow-up Phase

Eyes with OCT center point thickness < 200 microns or >= 300 microns will have completed the study at the baseline visit. Only subjects with at least one eligible eye will be continued in the follow-up phase.

As noted above, patients with both eyes found to be ineligible on OCT for follow-up do not need to have fundus photographs taken or E-ETDRS acuity testing if it has not been done already, provided retinopathy level of the study eye(s) is level 35 or greater.

CHAPTER 3.
FOLLOW-UP PHASE

3.1 Subject Eligibility for Follow-up Phase

Subjects who have at least one eye having OCT center point thickness between 200 and 299 microns and meeting the other study eligibility criteria will enter the follow-up phase.

Final determination of eligibility for the follow-up phase is dependent on Reading Center confirmation. If the Reading Center determines that the baseline OCT center point thickness is outside of the above range (e.g., automated algorithm resulting in a central point thickness of 200 to 299 microns judged to have incorrect placement of lines created by the computer algorithm and determined by manual caliper measurement not to have a central point thickness of 200 to 299 microns), the subject will not be included in the follow-up phase of the study. If the Reading Center judges the baseline OCT to be ungradeable, the subject will be asked to revisit the clinic and have the OCT repeated as soon as possible.

3.2 Visit Schedule

Study-specified follow-up visits will occur at 12 months $\pm$ 8 weeks and at 24 months $\pm$8 weeks. Additional visits may occur as required for usual care of the study participant. If at a nonprotocol visit, treatment is to be given for diabetic macular edema, study data will be collected (see section 3.4).

3.3 Testing Procedures at 12-Month and 24-Month Interval Protocol Visits and any Interim Visit When Treatment for Macular Edema is Planned ("Treatment Visit")

The following procedures will be performed on the study eye at the 12-month and 24-month visits 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. A grid in section 1.3 summarizes the testing performed at each follow-up visit.

1. E- ETDRS visual acuity testing on both eyes (with refraction on the study eye(s)).
2. Slit lamp examination and dilated fundus examination.
3. ETDRS protocol stereoscopic fundus photography.
   - ETDRS 3-fields (1M, 2, 3M).
4. OCT
   - Performed on the study eye(s) at the 12 and 24 month visits ***after*** the investigator assesses whether DME involving the fovea is present on clinical examination and whether DME involving or threatening the fovea warrants treatment.
   - Should be performed using the same OCT machine version used at baseline (e.g., OCT3 or higher used throughout the study for a particular patient).
   - If OCT center point thickness at the 12-month visit is at least 300 microns *and* increased by at least 50 microns from baseline to follow-up, eye will discontinue follow-up (if subject has one study eye, the subject will have completed the study).
   - All efforts will be made to reduce the chances of an ungradeable OCT scan. The OCT technicians will be instructed to aim for a signal strength of at least 6, and standard

deviation of center point less than 10% of center point. However, if the technician determines the scan is acceptable, it may be submitted with a lower signal strength or higher standard deviation. If an adequate scan cannot be obtained, the site should evaluate the size of the pupils and, if indicated, dilate the pupils again and then repeat the scan.

5. Measurement of blood pressure.

6. HbA1c
   - If an HbA1c test result is available from the prior 3 months, it does not need to be repeated at these visits.

3.4 Testing Procedures at Interim Visits When Treatment for Macular Edema is Planned ("Treatment Visit")

Subjects may have visits at times other than 12 months and 24 months at investigator discretion.

If the investigator determines that macular edema is present warranting treatment, prior to treatment, all tests should be performed on the study eye as at the month 12 and month 24 visits, including OCT, visual acuity, and fundus photographs (3-fields).

If a study eye receives treatment for edema in between protocol visits without obtaining an OCT, OCT will NOT be obtained at a later visit. Further follow-up on this eye will not occur.

3.5 Treatment Assessment

At the 12 and 24-month visits, the investigator will assess whether DME involving the fovea is present on clinical examination and whether DME involving or threatening the fovea warrants treatment, ***prior to obtaining the follow-up OCT***. If at any interim visit an initial treatment for macular edema is undertaken, then that interim visit is considered a "treatment visit" with all tests obtained as would be obtained at a 12-month interval visit. This includes OCT after the clinical examination to assess DME.

3.6 Completion of the Study

An eye will have completed the follow-up phase of the study when at least one of the following conditions occurs:

1. Study eye OCT center point thickness at 12-month visit is at least 300 microns *and* increased by at least 50 microns from baseline.
2. Treatment for macular edema in the study eye prior to 24 months.
3. Completion of the 24-month follow-up visit.

CHAPTER 4.
MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

4.1 Diabetic Retinopathy Management

Diabetic retinopathy management is left to the study participant's ophthalmologist. Treatment for DME is not considered to be part of the study.

4.2 Diabetes Management

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

4.3 Study Participant Withdrawal and Losses to Follow-up

A study participant 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 12 and 24-month examination visits will be performed. Ownership of the data collected up until the time of withdrawal is retained by the DRCR network.

Subjects who withdraw will not be replaced.

4.4 Discontinuation of Study

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

4.5 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 subject in the first month after enrollment. Additional phone contacts from the Coordinating Center will be about 6 months and 18 months after enrollment for active participants to facilitate the scheduling of the subjects for follow-up visits and to determine if any treatment for diabetic macular edema was given since the last study visit. A study participant newsletter will be sent twice a year. A study logo item valued under $10 may be sent once a year.

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

4.6 Subject Reimbursement

Subjects will be paid $25 per completed visit for the three protocol visits (baseline, one year, and two years; maximum is $75). Subjects not eligible for follow-up will be paid $25 for the baseline visit only. Subjects will be paid $25 for a completed Treatment Visit if they have completed the study. Payment will be made from the Coordinating Center following each visit. If there are extenuating circumstances, additional funds may be provided for travel of follow-up

visits if expenses exceed $25 and the patient will be unable to complete the follow-up visit without the reimbursement of the travel expenses.

CHAPTER 5.
ADVERSE EVENTS

5.1 Events to Be Reported

An adverse event is any untoward medical occurrence in a study participant, irrespective of whether or not the event is considered related to the study. Since the study does not involve an intervention, adverse event reporting will be limited to those events that are possibly related to study procedures and are unanticipated.

An *Unanticipated Adverse Event* is defined as an adverse event caused by or associated with a procedure, if that effect or problem was not previously identified in nature or severity.

There are no foreseeable unanticipated adverse events associated with the three study procedures: visual acuity testing, OCT, and fundus photography.

5.2 Reporting Requirements for Adverse Events

Any reportable adverse event must be reported to the Coordinating Center within one working day of occurrence. A written report on such an event will be sent to the Coordinating Center within five days of occurrence, stating a description of the reaction, any required intervention, and the outcome. Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB. Contact information for the Coordinating Center is located in the Study Directory.

5.3 Risks and Discomforts

5.3.1 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, but are part of standard care.

5.3.2 Fundus Photography

Fundus photography carries no risk. The camera flash may cause temporary discomfort for the study participant.

5.3.3 Optical Coherence Tomography

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

CHAPTER 6.
STATISTICAL METHODS

The estimation of sample size and statistical analysis plan are summarized below and detailed in separate documents. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in section 6.2 contains the framework of the anticipated final analysis plan, which will supersede section 6.2 when it is finalized.

6.1 Sample Size

A sample of approximately 220 patients will be enrolled with OCT center point thickness 200-299 microns in at least one eye. As an observational study, the primary analysis will consist of the estimation of the event rate for several outcomes. An additional sample of 100 subjects with no background diabetic retinopathy or microaneurysms only (level 20) in one or both eyes will be enrolled. The primary analysis of these patients consists of estimation of mean retinal thickness and confidence intervals.

The ETDRS suggested that 25% of eyes without macular edema involving or threatening the macular center at baseline will progress to diabetic macular edema that involves or threatens the macular center over 3 years.[26] This suggests that approximately 15% will progress in two years.

For the primary outcome (e.g., progression to OCT center point thickness of at least 300 microns *and* increase of 50 or more microns from baseline or treatment for DME), the table below shows the width of a 2-sided 95% confidence interval for various proportions of varying sample sizes.

	Half-width of 2-sided 95% CI			
Expected Proportion	**N=50**	**N = 100**	**N = 200**	**N = 400**
0.50	0.139	0.098	0.069	0.049
0.40	0.136	0.096	0.068	0.048
0.30	0.127	0.090	0.064	0.045
0.25	0.120	0.085	0.060	0.042
0.20	0.111	0.078	0.055	0.039
0.15	0.099	0.070	0.049	0.035
0.10	0.083	0.059	0.042	0.029

A two-year follow-up period should allow sufficient time for the development of the primary and secondary outcome variables since the ETDRS suggested that 25% of people without macular edema that involves or threatens the macular center at baseline will progress to diabetic macular edema that involves or threatens the macular center over 2 years.[26]

Sample size has been established so that the half-width of a 2-sided 95% confidence interval for the progression proportion will be less then 0.05. The resulting sample size from the above table is 200 subjects. Therefore, 220 subjects will be enrolled in the study to account for 10% lost to follow-up. Since the final sample size will include subjects with two study eyes, the resulting confidence interval will be narrower.

Primary analysis of patients enrolled with no diabetic retinopathy or minimal non-proliferative diabetic retinopathy (microaneurysms only consistent with level 20) in one or both eyes includes construction of 95% confidence intervals for the retinal thickness estimates based on standard deviation from healthy controls, which is reported as 20 microns.[18] That same study described a standard deviation of 14 microns for 30 patients with diabetes and no retinopathy.[18] A desired 95% confidence interval of 10 microns would result in a sample size of 62 eyes using the more conservative standard deviation estimate from healthy controls.

Sample Size Required to Obtain the Desired Half-Width of a 95% Confidence Interval

	Half-Width of 95% Confidence Interval		
Standard Deviation	**5**	**10**	**15**
15	35	9	4
20	62	16	7
25	97	25	11
30	139	35	16
35	189	48	21
40	246	62	28
50	385	97	43

A secondary objective using data from the baseline examination is to explore the hypothesis that retinal thickness increases with increasing duration of diabetes in patients with no or minimal retinopathy. Another hypothesis that retinal thickness increases as eyes evolve through the early stages of background retinopathy can be explored by stratified analysis of thickness based on the presence or absence of microaneurysms. Sample size estimates for these secondary objectives are based on 90% power to detect a difference between two groups. A sample size of 86 eyes is needed for each subgroup to detect a difference of 10 microns. An interim analysis to determine the standard deviation of subjects with no or minimal retinopathy will be performed after about 50 subjects. Additional subjects in this subgroup may be enrolled if variance in retinal thickness is greater than predicted.

Sample Size Needed Per Subgroup for 90% Power to Detect a Difference

	Difference in Means (microns)						
Estimated Standard Deviation	**5**	**10**	**15**	**20**	**30**	**40**	**50**
15	191	49	23	13	7	5	4
20	338	86	39	23	11	7	5
25	527	133	60	34	16	10	7
30	758	191	86	49	23	13	9
40	1346	338	151	86	39	23	15

Alpha = 0.05 (2-sided)

6.2 Analysis Plan

6.2.1 Development of Macular Edema

Fundus photographs will provide gradings of level of retinopathy and confirmation of absence of macular edema at baseline and presence of macular edema at follow-up.

The proportion of eyes developing diabetic macular edema involving the center of the retina or treated for DME between baseline and follow-up visits will be computed and a 95% confidence interval will be constructed.

The risk of developing DME will be compared by baseline OCT thickening and retinopathy grade.

Change in retinal thickening will be a secondary outcome measure of importance. For the study eye, the percent change in OCT retinal thickening from baseline will be computed.

6.2.2 Retinal Thickness in Eyes with No or Minimal Retinopathy

The mean (SD) thickness of the center point and other subfields will be computed.

If there are sufficient data, separate assessments will be made for eyes with no retinopathy and eyes with minimal non-proliferative diabetic retinopathy (level 20). Exploratory analyses will evaluate the effect of duration of diabetes, type of diabetes, and other factors on the retinal thickness measurements.

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