Diabetic Retinopathy Clinical Research Network

Protocol #1A

A Pilot Study of Laser Photocoagulation for Diabetic Macular Edema

Version 1.1

April 16, 2003

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CHAPTER 1
INTRODUCTION

1.1 General Overview

The Diabetic Retinopathy Clinical Research Network (DRCRnet) was formed to conduct clinical trials and epidemiological studies for diabetic retinopathy.

As part of the establishment of the network, it is necessary to standardize data collection methods, testing procedures, and treatment techniques for use in the anticipated multiple protocols to be conducted by the network. One of the treatment techniques requiring standardization is laser photocoagulation treatment of diabetic macular edema. To accomplish this goal, a protocol has been developed to enroll patients with diabetic macular edema who require laser treatment. Procedures to be conducted by standardized protocols include refraction,[1] visual acuity testing,[2] fundus photography,[3] fluorescein angiography,[4] optical coherence tomography (OCT) and laser photocoagulation[5] One of the benefits from having a structured protocol will be that the outcome data using the standardized techniques can be used for sample size estimations in future protocols. This is particularly true for OCT for which we need to develop standard methods to assess changes in groups of patients and for which there are limited longitudinal data, especially in groups of patients.[6]

The conduct of this study provides the opportunity not only to collect data on a standardized laser protocol commonly used in current clinical practice but also to collect pilot data evaluating a new laser technique. The 'current practice' laser protocol, modified from the ETDRS treatment protocol,[5, 7-9] involves focal/grid photocoagulation to areas of macular thickening with leaking MA, diffuse leakage or nonperfusion (modified-ETDRS technique). There is extensive evidence supporting the efficacy of ETDRS laser photocoagulation technique for the treatment of macular edema. The alternative technique, called mild macular grid (MMG) photocoagulation, provides mild grid treatment using small, widely separated burns to the retina from 500 to 3000 microns (3500 microns temporally) from the macular center. This technique may potentially have fewer side effects, different edema resolution rate or prevention of future development of macular edema as discussed below. The study will use randomization to assign each patient to receive one of the two treatment methods.

For this protocol, participation will be open to all clinical sites that have the requisite equipment needed for the study and to all ophthalmologists who meet criteria to be a DRCR.net investigator. The sample size for the study will be dictated by the number of participating sites, with each site limited to the enrollment of a maximum of four patients or one patient per certified investigator, whichever is greater.

1.2 Protocol Goals & Questions

This pilot study is not designed for hypothesis testing, but rather for hypothesis generation, for gathering outcome data, and for standardization of network protocols as discussed above.

With regard to hypothesis generation, some of the important issues that the protocol can address in terms of the modified-ETDRS macular photocoagulation technique include:

1) Evaluate the risk of moderate visual loss in patients treated with the modified-ETDRS technique which incorporates the lighter treatment approach in common clinical practice today.

2) Evaluate outcome rates in today's patient populations with improved glycemic control as compared with the outcomes derived from the classic reference studies such as DRS and ETDRS, which were performed when glycemic control was generally less stringent.

3) Gain experience and evaluate usefulness of objective retinal thickness measurements (e.g. OCT and modified photographic methods) in prospective, longer duration, diabetic macular edema studies.

4) Evaluate improved photographic grading methods compared with classic reference studies.

With regard to hypothesis generation, some of the important issues that data from the group of patients randomized to mild macular grid (MMG) treatment can address include:

1) Evaluate risk of moderate visual loss and side effects from a treatment approach that incorporates:
   - lighter treatment of areas of retinal thickening (i.e. without focal microaneurysm treatment) and
   - potential distant effects of additional light grid treatment (i.e. treatment to macular areas without thickening)

2) Evaluate potential for prevention of macular edema onset in areas of initially unthickened retina that were treated with light grid treatment

3) Evaluate number of treatments required to resolve macular edema as compared with the modified-ETDRS technique

1.3 Background Information on Diabetic Macular Edema

Diabetic retinopathy is a disorder of major public health importance, accounting for the majority of visual loss among working age Americans. Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) estimate that after 15 years of known diabetes, the prevalence of diabetic macular edema is approximately 20% in patients with type 1 diabetes mellitus (DM), 25% in patients with type 2 DM who are taking insulin, and 14% in patients with type 2 DM who do not take insulin[10] The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that moderate vision loss, defined as a doubling of the visual angle (e.g., 20/20 reduced to 20/40), can be reduced by 50% or more by focal/grid laser photocoagulation according to ETDRS protocol.[5] Although several treatment modalities are currently under investigation, the only demonstrated means to reduce the risk of vision loss from diabetic macular edema are ETDRS laser photocoagulation, as demonstrated by the ETDRS, and intensive glycemic control, as demonstrated by the Diabetes Control and Complications Trial (DCCT) [11] and the United Kingdom Prospective Diabetes Study (UKPDS).[12] In the DCCT, intensive glucose control reduced the risk of onset of diabetic macular edema by 23% compared with conventional treatment. Long-term follow-up of patients in the DCCT show a sustained effect of intensive glucose control, with a 58% risk reduction in the development of diabetic macular edema for the DCCT patients followed in the Epidemiology of Diabetes Interventions and Complications Study.[13]

1.4 Rationale for modified-ETDRS Treatment

ETDRS treatment for diabetic macular edema involved direct focal treatment to discrete lesions between 500 microns and 3000 microns from the center of the macula that were thought to be

causing retinal thickening or hard exudates with or without "grid" treatment to other macular areas of retinal thickening.[7] or non-perfusion. The lesions treated focally included microaneurysms, identified on fluorescein angiography, that either filled or leaked, intraretinal microvascular abnormalities (IRMA), or pruned capillaries that leaked fluorescein. Grid treatment was applied in the ETDRS to areas of thickened retina that showed diffuse fluorescein leakage or capillary dropout. Areas of non-perfusion in the macula could be treated with grid at the discretion of the treating ophthalmologist. Areas that had both discrete lesions and diffuse leakage or capillary dropout would receive a combination of direct focal and grid treatment. A full description of ETDRS treatment for diabetic macular edema is detailed in ETDRS report #4. In the ETDRS, focal/grid treatment resulted in a decrease in retinal thickening, a decreased risk of moderate vision loss, and, in some cases, an increased likelihood of moderate vision gain.

The mechanism of action of focal/grid laser photocoagulation in the ETDRS is not fully understood; however, it is clear that the retinal pigment epithelium (RPE) absorbs the majority of the laser energy and thermal injury occurs at the level of the RPE.[14, 15] Studies have shown that photocoagulation eventually results in retinal and apparent RPE atrophy 200-300% larger than the original laser spot size.[16, 17] These areas of expanded atrophy can lead to loss of central vision, central scotomata, and decreased color vision. Consequently, many retinal specialists today tend to treat with lighter, less intense laser burns than originally specified in the ETDRS.[18-21]

In addition to the concern regarding the spread of intense laser burns, there are a number of other reasons that retinal specialists today have modified the treatment procedures originally specified in the ETDRS protocol. These reasons include the advent of new lasers, a desire to develop an easier method to deliver macular treatment, and the clinical observation that different techniques, such as focal or grid treatment alone, are apparently similar in beneficial effect as the original ETDRS treatment protocol.[19, 22]

There is a need, therefore, to evaluate the efficacy of treatments that have come into common clinical use. In addition to evaluating the efficacy of these modified treatment protocols, it is important that we develop a common treatment protocol for the DRCR.net upon which all investigators can agree.

1.5 Rationale for Mild Macular Grid (MMG)

There are several reasons for evaluating the MMG treatment approach. Lighter treatment techniques hold theoretical benefits such as reduced scotomata, less burn spread, decreased epiretinal membrane formation, less likelihood to rupture Bruchs' membrane, etc.[23-27] To date such therapeutic approaches have not been rigorously evaluated in large clinical trials. MMG does not focally treat microaneurysms.

Beneficial effects of photocoagulation may be expected even without treatment of focal microaneurysms. Grid treatments alone have been evaluated in limited trials with evidence of reduced macular edema. Indeed, in patients with diffuse macular edema and few or no microaneurysms, the well-proven ETDRS treatment approach employs only a grid.[22, 25-27]

It is also clear that laser treatments alter biochemical processes within the retinal pigment epithelium and studies have suggested that such stimulation may account for some of the therapeutic effect.[28-32]

Thus, resolution of macular edema following laser photocoagulation is not solely dependent on focal treatment of microaneurysms.

Since laser treatments alter biochemical processes within the retinal pigment epithelium and studies have suggested that such stimulation may have therapeutic benefit, MMG may stimulate more RPE or RPE that is healthier than would be treated by standard focal treatment. This might increase the beneficial biochemical changes or release of helpful factors.

Macular treatment in areas without retinal thickening has been used in preliminary light intensity diode laser studies with reported effectiveness.[19, 22] The burns in the MMG protocol are well-separated and light in intensity. This should have little effect on visual function. It is well established that panretinal (scatter) photocoagulation can have marked therapeutic effect in areas distant to the laser burns themselves.[33]

It is possible that the light MMG burns throughout the macula may have a similar effect on distant areas of retinal thickening in the macula, thus possibly increasing the therapeutic effect. It is also possible that increased RPE stimulation or improved retinal oxygenation provided by the use of the MMG approach, which treats areas of the macula that are not treated by the standard ETDRS approach, may help prevent subsequent onset of macular edema in these areas.

There is also clear evidence that macular edema may exist that is not appreciated clinically. These subclinical areas are classically not treated. The MMG approach would result in treatment of these areas and thus may have added benefit.

1.6 Current Study Overview

In brief, the study protocol involves the enrollment of patients $\geq$18 years of age who have DME involving or threatening the center of the macula and who have not had prior focal/grid laser photocoagulation for DME. These are patients for whom the standard of care would be to treat with laser photocoagulation. Eligible eyes will be randomly assigned to receive either the modified-ETDRS technique or the MMG technique. The initial laser treatment protocol for each technique is described in section 5.1. The criteria for and protocol for retreatments are described in section 5.1.1. Outcome assessments will include Optical Coherence Tomography (OCT), fundus photography, fluorescein angiography and standardized best-corrected visual acuity.

The study consists of two phases: **Phase 1** (the primary study), which consists of the first 12 months of follow up, during which a structured protocol is followed; and **Phase 2,** which consists of the second and third years of follow up, during which the management of DME can include techniques other than laser photocoagulation, at discretion of the investigator.

During **Phase 1**, follow-up visits will occur at 15 weeks (3.5 months) $\pm$14 days, 34 weeks (8 months) $\pm$ 28 days, and 52 weeks (12 months) $\pm$ 28 days. The primary outcome for phase 1 is at 12 months. The primary study objectives of Phase 1 include:

- Develop standardized study procedures for future DME studies
- Obtain outcome data (e.g. changes in retinal thickness, area of retinal thickening, area of hard exudate, need for retreatment, onset of new areas of DME and changes in visual acuity) following use of the modified-ETDRS photocoagulation technique for patients with DME and various levels of retinopathy severity.
- Collect pilot data using the MMG technique to determine whether a subsequent large scale definitive trial should be conducted

Phase 2 (2nd and 3rd years of follow up) is being conducted to collect data on, and generate hypotheses from, the long-term outcome of DME, irrespective of treatment received.

- Protocol visits will occur at 2 years ± 8 weeks and 3 years ± 8 weeks.

During this phase of the study, therapies other than laser photocoagulation may be used to treat DME at the investigator's discretion. Because treatment other than photocoagulation will be allowed after one year, 'pure' results regarding outcomes with each laser technique cannot be obtained in all groups, but will be available in a subset of patients. The data are being collected at relatively low cost and no risk over and above usual care. Therefore, the collection of potentially hypothesis-generating data from exploratory analysis is justified and could be important in designing future studies. Interpretation of the results of the above analyses will be complicated by the lack of a standardized protocol with regard to which patients receive treatment and what treatment is provided. Therefore, the results will be interpreted with caution. The phase 2 data collection may be useful for the following:

1) Evaluation of retreatment rates in patients who responded to laser such that no additional treatment was required at 12 months. *This is a long term analysis on a "pure" group of patients and will provide important information on the DME recurrence rate and need for retreatment in study eyes of those patients whose DME improved with either of the two protocol-specified treatments received in Phase 1 such that further treatment was not necessary at the 12-month visit.*

2) Provide long-term safety data for MMG. *This is important due to the less well studied nature of MMG, especially over the long term.*

3) Provide long-term outcome data on current standard treatment (modified ETDRS laser) in today's patient populations to assist in powering future studies that will require at least 3 years of follow up.

4) Provide data on outcome of intravitreal steroids in patients in whom laser treatment is not successful. *For many patients who still have DME at 12 months, it is anticipated that intravitreal steroids will be administered. The continued follow up of these patients will provide an opportunity to explore the effect of the steroids on retinal thickness and visual acuity.*

Schedule of Study Visits and Examination Procedures

		Follow-up Visits (timed from randomization, months)				
		Phase 1			Phase 2	
	Baseline	3.5	8	12	24	36
ETDRS refraction and visual acuity OU	x	x	x	x	x	x
Fundus photos OU	7F[a]	3F[a]	3F[a]	7F[a]	7F[a]	7F[a]
ETDRS fluorescein angiography OU	x			x		
OCT OU	x	x	x	x	x	x
Eye Exam[b]	x	x	x	x	x	x
Blood pressure	x			x	x	x
HbA1c[c]	x			x	x	x
BUN, creatnine, microalbumin[c]	x					
Fasting lipid profile[d]	x					

a= post-laser photos (only field 2 stereo) to be done in addition after any laser treatment.

b=exam performed according to investigator's usual routine

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

d=performed after overnight fast; does not need to be repeated if LDL and triglyceride results are available in prior 6 months (at baseline, can be performed within 3 weeks after randomization)

CHAPTER 2
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Identification of Eligible Subjects and Obtaining Informed Consent

A minimum of 200 subjects are expected to be enrolled with a goal to enroll an appropriate representation of minorities. Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, informed consent will be obtained. For subjects who are considered potentially eligible for the study based on a routine-care exam, the study protocol will be discussed with the patient by a study investigator and clinic coordinator. The patient will be given the Informed Consent Form to read.

Consent will be given in two stages. The initial stage will provide consent to complete any of the screening procedures needed to assess eligibility that have not already been performed as part of a usual-care exam. The second stage will be obtained prior to randomization and will be for participation in the study. A single consent form will have two signature lines for the patient: one for the patient to give consent to the completion of the screening procedures and one for the patient to give consent for the randomized trial.

Patients who are found to be eligible will be encouraged to discuss the study with family members, friends, or their personal physician before deciding whether to participate in the study. Patients who decide to participate will have signed both stages of the consent form prior to randomization for participation in the study. Patients will be provided with a signed copy of the Informed Consent Form.

Once a patient is randomized, that patient will be counted regardless of whether the assigned treatment is received or not. Thus, the investigator must not proceed to randomize a patient until he/she is convinced that the patient will accept either treatment group assignment.

2.2 Eligibility Criteria

2.2.1 Subject-level Criteria

1. Age >= 18 years
    - *Patients <18 years old are not being included because DME is so rare in this age group that the diagnosis of DME may be questionable.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
    - *Any one of the following will be considered to be sufficient evidence that diabetes is present:*
        a. *Current regular use of insulin for the treatment of diabetes*
        b. *Current regular use of oral antihyperglycemia agents for the treatment of diabetes*
        c. *Documented diabetes by ADA guidelines (see DRCR.net Procedures Manual)*
3. No history of renal failure requiring dialysis or renal transplant.
4. No condition that in the opinion of the investigator would preclude participation in the study (e.g., unstable medical status including blood pressure and glycemic control;
    - *Patients in poor glycemic control who recently initiated intensive insulin treatment (a pump or multiple daily injections) or plan to do so in the next 3 months should not be enrolled.*

5. Ability and willingness to provide informed consent.
6. No expectation that subject will be moving out of the area of the clinical center to an area not covered by another clinical center during the next 12 months.

2.2.2 Study Eye Criteria

At least one eye must meet all of the following criteria:

1. Best corrected ETDRS visual acuity score >= 19 letters (approximately 20/400 or better).
2. Definite retinal thickening due to diabetic macular edema based on clinical exam at or within 500 microns of the macular center for which the investigator believes laser photocoagulation is indicated.
3. A thickness of 250 microns or more in the central subfield OR a thickness of 300 microns or more in any one of the four subfields directly adjacent to the central subfield on OCT.
4. No prior focal/grid laser photocoagulation in the macula.
5. No prior medical treatment for DME (e.g., intravitreal/peribulbar steroids).
6. No panretinal scatter photocoagulation (PRP) within prior 4 months.
7. No anticipated need for PRP within next 4 months.
8. No major ocular surgery (including cataract extraction, any other intraocular surgery, scleral buckle, glaucoma filter, cornea transplant, etc.) within prior 6 months.
9. No Nd:YAG laser capsulotomy within prior 2 months.
10. Macular edema is not considered to be due to a cause other than diabetic macular edema
    - An eye should not be considered eligible (1) if the macular edema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggests that vitreoretinal interface disease (eg. vitreo-retinal traction or epriretinal membrane) is the primary cause of the macular edema.
11. Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photos.
12. No ocular condition (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the first 12 months of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome).
    - Glaucoma per se is not an exclusion.

A patient may have two "study eyes" only if both are eligible at the time of randomization. An eye that becomes eligible after randomization will not be considered a study eye for purposes of data analyses or treatment decisions although information is being gathered on all eyes)

2.3 Screening Evaluation and Baseline Testing

2.3.1 Historical Information

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

2.3.2 Examination Procedures

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

If a procedure has been performed (using the study technique) 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 Manual. Visual acuity testing, fundus photography, fluorescein angiography, OCT, and ocular exam will be performed by certified personnel.

1. ETDRS protocol refraction and visual acuity testing in both eyes *(must be done on day of randomization)*
   - Acuity testing will be performed using the electronic ETDRS testing procedure. If not available, standard ETDRS charts at 4 meters (plus 1 meter testing for low vision) will be used.
2. OCT of both eyes *(done within 21 days of randomization).*
   - Must be performed using the same OCT machine version used at baseline (eg. OCT1 or OCT2 or OCT3 used throughout the study for a particular patient)
3. Ocular examination including dilated ophthalmoscopy in both eyes *(done within 21 days of randomization).*
4. ETDRS protocol 7-standard field stereoscopic fundus photography (fields 1M, 2, 3M, 4, 5, 6, 7) in both eyes *(done within 21 days of randomization).*
5. ETDRS fluorescein angiography (study eye first, then fellow eye) *(done within 21 days of randomization)*
   - For patients with two study eyes, please refer to the Procedures Manual for sequence instructions.
6. Measurement of blood pressure *(done within 21 days of randomization)*
   - Measured in sitting position after patient has been sitting for at least 5 minutes

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

In most cases, assessment of eligibility will require at least two visits. For this reason, maximum time windows from the completion of each procedure above to the day of randomization have been established.

Procedure	Maximum Time from Completion to Randomization
ETDRS Visual Acuity Testing	0 days*
Ophthalmic Exam	21 days
OCT	21 days
ETDRS Fundus Photographs	21 days
ETDRS Fluorescein Angiography	21 days

* *must be done on day of randomization*

2.3.3 Laboratory Tests

1. HbA1c, BUN, creatinine
2. Lipids (fasting LDL and triglycerides)
3. Microalbumin

HbA1c, BUN, creatinine, and microalbumin testing does not need to be repeated if available in the prior 3 months and lipid testing does not need to be repeated if available in the last 6 months.

If all of the required laboratory test results are not available at the time of randomization, the patient may be enrolled, but the tests will be obtained within 3 weeks after randomization.

Whenever possible, the HbA1c will be measured using the DCCT method at a laboratory that is certified for the national glycohemoglobin standardization program.

2.4 Enrollment/Randomization of Eligible Patients

1. The Coordinating Center will construct separate master randomization lists for patients with one study eye and for patients with two study eyes
   - For patients with one study eye, the randomization will be stratified according to the presence/absence of unthickened subfields on OCT. Among patients with at least one unthickened subfield (expected to be a majority), the randomization also will be stratified by site.
   - For patients with two study eyes (both eligible at time of enrollment), one eye at random will be selected to receive one treatment technique and the other eye will receive the other treatment technique.
2. Prior to randomization, the patient's understanding of the trial, willingness to accept either treatment assignment, and commitment to the follow-up schedule should be reconfirmed. The patient must then sign the enrollment line on the informed consent document.
3. The photocoagulation treatment must commence on the day of randomization; therefore, a patient should not be randomized until the investigator and patient are ready to begin the laser treatment.
4. If there is an equipment failure or other reason why the laser cannot be given on the day of randomization, treatment should be given as soon as possible.
   - ETDRS refraction and acuity testing will need to be repeated on the day the laser treatment begins.
   - OCT, fundus photography, and fluorescein angiography will only need to be repeated if the maximum time limits in section 2.4.2 are exceeded.

2.5 Baseline Photocoagulation

Each study eye is randomly assigned to receive either (a) modified-ETDRS photocoagulation or (b) mild macular grid photocoagulation.

The initial treatment session for laser photocoagulation may be performed over single or multiple sittings, as long the entire treatment session is completed within 6 weeks of beginning the treatment session. Subsequent retreatment should then be deferred until at least the 3.5 month visit.

Chapter 5 describes the photocoagulation treatment techniques.

2.6 Post-photocoagulation Photographs

During phase 1, a Field 2 stereo pair will be taken following photocoagulation in all patients.

- Post-treatment photos will be taken at the **end of each sitting**.

CHAPTER 3
FOLLOW-UP VISIT SCHEDULE AND PROCEDURES

3.1 Follow-up Visit Schedule

Below is the visit schedule and time windows for each phase of the study. A visit is not considered missed until the next visit window opens. **All attempts should be made to complete a visit even after the visit window closes.**

Phase 1 (0-12 Months)

- 15 weeks (3.5 months) ± 14 days
- 34 weeks (8 months) ± 28 days
- 52 weeks (12 months) ± 28 days

Phase 2 (13-36 Months)

- 2 years ± 8 weeks
- 3 years ± 8 weeks

3.2 Follow-up Visit Testing and Procedures

The following procedures are performed at each protocol visit unless otherwise specified. The procedures are detailed in the DRCR.net Procedures Manual. Visual acuity testing, fundus photography, fluorescein angiography, OCT, and ocular exam will be performed by certified personnel. A table in chapter 1 (section 1.6) summarizes the procedures to be performed at each visit.

1. ETDRS protocol refraction and visual acuity testing in both eyes.
   - Acuity testing will always be performed by a certified, masked tester
   - If a masked tester is unavailable, testing may be done by an unmasked tester (this will be considered a protocol deviation).
2. OCT in both eyes.
   - Must be performed using the same OCT machine version used at baseline (eg. OCT1 or OCT2 or OCT3 used throughout the study for a particular patient)
3. Ocular examination including dilated ophthalmoscopy in both eyes.
4. Stereoscopic fundus photography in both eyes.
   - ETDRS 3-fields (1M, 2, 3M) at the 3.5-month and 8-month visits
   - ETDRS 7-fields (1M, 2, 3M, 4, 5, 6, 7) at 12, 24, and 36 month visit
   - ETDRS field 2 following any DME photocoagulation session
5. Measurement of blood pressure (12, 24, and 36 month visits only).
   - Measured in sitting position after patient has been sitting for at least 5 minutes
6. HbA1c (12 24, and 36 month visits only).
   - If a HbA1c test result is available from the prior 3 months, it does not need to be repeated at this visit.
7. ETDRS fluorescein angiography (12-month visit only, if not medically contraindicated).

The fundus photographs, fluorescein angiograms, and OCT will be sent to the Fundus Photograph Reading Center for grading.

3. Assessment of Need for Additional Photocoagulation for DME

At each visit the investigator will assess whether persistent, recurrent, or new DME is present that warrants additional photocoagulation.

The criteria for determining whether retreatment is indicated are described in section 5.1.1. Section 5.1.1 also provides the retreatment protocol.

3.4 Non-protocol Visits

Additional visits can be performed at any time based on the perceived need for such visits by the study investigator. A data form will be submitted for each non-protocol visit.

CHAPTER 4
MISCELLANEOUS CONSIDERATIONS IN FOLLOW UP

4.1 Non-protocol Treatment for DME

During Phase 1 (prior to the 12 month visit), the patient should receive no treatment in the study eye for DME other than the protocol-defined laser treatment.

During Phase 2 (after the 12 month visit), non-photocoagulation therapies for DME may be given at the discretion of the investigator. This includes treatment that might be received as part of another research study (see section 4.6). Any additional laser photocoagulation of the study eye will follow the retreatement protocol described in chapter 5.

4.2 Panretinal Photocoagulation

PRP can be given at any time if it is indicated in the judgment of the investigator. As part of the eligibility criteria, at the time of enrollment patients are not expected to need PRP within 4 months. In general, PRP should not be given if the patient has less than severe NPDR. In general, PRP should be given promptly for previously untreated eyes exhibiting PDR with high-risk characteristics.

4.3 Diabetes Management

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

4.4 Patient Withdrawal and Losses to Follow up

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

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

4.5 Discontinuation of Study

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

4.6 Participation in Other Studies Prior to the End of Three-year Follow Up

The Steering Committee may decide (with concurrence of the Data and Safety Monitoring Committee) to permit patients to participate in a new DRCR.net or other study during Phase 2 of this study. If the patient enters another research study, data will still be collected during Phase 2 of this current study.

4.7 Contact Information Provided to the Coordinating Center

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

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

4.8 Patient Reimbursement

The study will be paying $25 per completed visit for the randomization visit and follow up visits at 3.5, 8, 12, 24 and 36 months (6 visits = maximum payment of $150) to cover travel and other visit-related expenses. Payment will not be made for missed visits. Payment will be made following each visit from the Coordinating Center.

CHAPTER 5
PHOTOCOAGULATION TREATMENT

5.1 DME Laser Treatment Techniques

As the initial laser treatment in the study eye, each patient is randomly assigned to receive either (a) modified-ETDRS focal/grid photocoagulation or (b) mild macular grid photocoagulation.

Burn Characteristic	Focal / Grid Photocoagulation (modified-ETDRS technique)	Mild Macular Grid Photocoagulation Technique
Focal Treatment	Focally treat all leaking MAs in areas of retinal thickening between 500 and 3000 microns from the center of the macula (but not within 500 microns of disk)	Not applicable
Change in MA Color with Focal Treatment	Not required, but at least a mild gray-white burn should be evident beneath all MAs	Not applicable
Burn Size for Focal Treatment	50 microns	Not applicable
Burn Duration for Focal Treatment	0.05 to 0.1 sec	Not applicable
Grid Treatment	Applied to all areas with diffuse leakage or nonperfusion within area described below for treatment	Applied to entire area described below for treatment (including unthickened retina)
Area Considered for Grid Treatment	500 to 3000 microns from the center of macula 500-3500 microns temporally from macular center (or to posterior edge of PRP temporally if that is less than 3500 microns temporally from macular center) No burns are placed within 500 microns of disk	500 to3000 microns superiorly, nasally and inferiorly from center of macula 500-3500 microns temporally from macular center (or to posterior edge of PRP temporally if that is less than 3500 microns temporally from macular center) No burns are placed within 500 microns of the disk
Burn Size for Grid Treatment	50 microns	50 microns
Burn Duration for Grid Treatment	0.05 to 0.1 sec	0.05 to 0.1 sec
Burn Intensity for Grid Treatment*	Barely visible (light gray)	Barely visible (light gray)
Burn Separation for Grid Treatment*	2 visible burn widths apart	200-300 total burns evenly distributed over the treatment area outlined above (approx. 2-3 burn widths apart)
Wavelength (Grid and Focal Treatment)	Green to yellow wavelengths	Green to yellow wavelengths

* see reference photographs in the Testing Procedures Manual
MA = microaneurysm

NOTES:

The investigator may choose any laser wavelength for photocoagulation within the green to yellow spectrum. The wavelength used will be recorded and any retreatment must use the same wavelength.

A treatment session can be given in single or multiple sittings at the investigator's discretion, as long as the entire treatment session is completed within 6 weeks. If treatment is given over more than one sitting, post-treatment photographs (field 2 stereo) will be taken at the **end of each sitting**.

5.1.1 Retreatment of DME

At each visit the investigator will assess whether persistent, recurrent or new DME is present that warrants additional photocoagulation.

It is generally expected that retreatment WILL be performed if, in the opinion of the investigator:

- DME has worsened from last scheduled visit.
- DME has recurred since last scheduled visit.
- New DME has arisen since last scheduled visit.
- Thickening at or within 500 microns of the macular center is present, unless there has been substantial improvement in macular edema from last scheduled visit in the opinion of the investigator (ie ≥50% decrease in total macular thickened area OR ≥50% decrease in retinal thickening (thickening is not retinal thickness, it is the difference between normal retinal thickness and observed retinal thickness) by OCT in the involved subfields (central or inner).

It is generally expected that retreatment WILL NOT be performed if, in the opinion of the investigator:

- DME has resolved.
- Center thickening present at the previous scheduled visit has resolved, unless there has been substantial worsening of DME elsewhere (eg >50% increase in total macular thickened area OR >50% increase in retinal thickening by OCT in central or inner subfields with previous thickening.

Retreatment in Phase 1 of the study should only occur at the 3.5 and 8 month visits.

For each patient, the same laser wavelength shall be used for all retreatments.

A retreatment session can be completed in single sitting or multiple sittings at the investigator's discretion, provided that the entire session is completed within 6 weeks. If retreatment is given over more than one sitting, post-treatment photographs (field 2 stereo) will be taken at the **end of each sitting**.

Retreatment of Patients in Modified-ETDRS Treatment Group

- All retreatment in patients assigned to the modified-ETDRS group, will use the same modified-ETDRS treatment technique.

Retreatment of Patients Mild Macular Grid Treatment Group

- The first retreatment in patients assigned to the MMG group will use MMG limited to only the area of retinal thickening.
- Second and subsequent retreatments in patients assigned to the MMG group will use the modified-ETDRS technique (which allows focal treatment to leaking microaneurysms in the area of retinal thickening).

The retreatment approach used will be recorded on a data collection form after each sitting.

5.2 Laser Scatter (Panretinal) Photocoagulation (PRP):

PRP can be given if it is indicated in the judgment of the investigator. Patients are not eligible for this study if it is expected that they will need PRP within 4 months. In general, PRP should not be given if the patient has less than severe NPDR. In general, PRP should be given promptly for previously untreated eyes exhibiting PDR with high-risk characteristics and can be considered for persons with PDR less than high-risk and for severe NPDR.

5.2.1 Burn Characteristics

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

CHAPTER 6
ADVERSE EVENTS

6.1 Events To Be Reported

Since the study does not involve an investigational drug or device, 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. The following occurrences will require reporting:

- Macular hemorrhage, foveal burn, choroidal neovascularization, chorioretinal anastomosis and Bruch's membrane break within 4 weeks of laser photocoagulation and thought to be possibly related to the photocoagulation treatment.
- A laser malfunction that produces harm to the patient.
- A deviation from the photocoagulation technique that produces visual loss (will be considered an unanticipated event).
- A severe reaction from fluorescein angiography resulting in hospitalization or death.

6.2 Definitions

Adverse events meeting the above reporting criteria will be reported with reference to: time and date of event, relationship to the device, severity, and final outcome.

The relationship of any reportable adverse event will be graded by a study investigator: on as possibly, probably, or definitely related to the study procedure.

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

6.3 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 front of the protocol as well as in the Study Directory.

6.4 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Committee will approve the protocol prior to its initiation and will be informed of all reportable adverse events as defined in section 6.1

6.5 Risks And Discomforts

6.5.1 Photocoagulation

Anesthetic drops may be used as a part of the photocoagulation procedure. Risks include allergic reaction, redness of the eye, and possible initially undetected corneal abrasion if the patient scratches the eye while it is numb. Retrobulbar injection of anesthetic may be used in some cases. Risks associated with this procedure are rare and may include: retrobulbar hemorrhage ; perforation

of the eye by the needle; damage to the optic nerve; double vision lasting up to 24 hours or more; drooping of the eye lid lasting up to 24 hours or more; difficulty speaking or breathing; lightheadedness/syncope/vasovagal response; allergy to any components of the injection; life threatening response due to the spread of anesthesia to the brain stem, resulting in epileptic fits, drowsiness, confusion, loss of verbalization, convulsions, respiratory arrest, or cardiac arrest.

Serious, but rare complications associated with photocoagulation and which may reduce vision include, but are not limited to: macular hemorrhage, foveal burn, choroidal neovascularization, chorioretinal anastomosis Bruch's Membrane break, creation of a scotoma , immediate or delayed increase in pressure inside the eye, damage to the optic nerve, damage to the iris, damage to the patient's lens or an intraocular lens, retinal hole, blindness, or loss of the eye.

6.5.2 Examination Procedures

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

6.5.3 Fundus Photography

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

6.5.4 Fluorescein Angiography

A yellow dye will be injected intravenously for this procedure. 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.

6.5. 5 Optical Coherence Tomography

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

CHAPTER 7
STATISTICAL CONSIDERATIONS

7.1 Sample Size and Power Considerations

The sample size for the study has been projected to be a minimum of 200 patients. This is a convenience sample based on a enrollment quota of four patients for most sites (sites with more than 4 investigators have a quota of one patient per investigator) and estimating that there will be approximately 50 participating sites.

For within-group dichotomous outcomes (e.g., worsening of visual acuity by 3 or more lines, improvement of visual acuity by 3 or more lines, resolution of edema), the table below shows the width of a 2-sided 95% confidence interval for various proportions for a sample size of 100.

Expected Proportion	Half-width of 2-sided 95% CI
.5	.098
.4	.096
.3	.090
.2	.078
.1	.059

For between group exploratory analyses, with a sample size of 200 and assuming no more than 10% loss to follow up and a 2-sided alpha of 0.05, the study will have 90% power to detect a difference in the change from baseline in central retinal thickness (as measured on OCT) between randomization groups of 50 microns assuming that the common standard deviation for the change from baseline is 100 microns. There are little data on which to estimate the standard deviation. Thus, one of the objectives of the study is to provide data that can be used to estimate sample size for future trials. For between-group dichotomous outcomes based on OCT, the study will have 90% power to detect a relative 50% difference between groups assuming that one group has an outcome rate of 50%.

7.2 Statistical Analysis

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

The primary outcome for phase 1 is at 12 months. Within each treatment group, point estimates and 95% confidence intervals will be computed for the following:

- Change in the central subfield of the ETDRS grid measured by OCT (in eyes with <250 microns mean thickness in the central subfield at baseline, the inner subfield with maximum mean thickness will be used instead).
- Change in area of retinal thickening or hard exudate (as measured by fundus photography).
- Change in retinal thickness in areas other than the central subfield.
- Change in the average diameter of the area of retinal thickening (the square root, expressed in disc diameters, of area expressed in disc areas) at each visit.

- Change in area of hard exudate at each visit.
- Frequency of epiretinal membrane formation as determined by the reading center using fundus photographs and OCT.
- Proportion of eyes retreated for macular edema at each visit.
- Change in retinopathy severity level on the ETDRS "eye scale".
- Change in visual acuity (mean, worsening by >=3 lines, improving by >=3 lines).

In exploratory analyses, the treatment groups will be compared using each of these variables. As a general rule, analysis of covariance models will be used for continuous variables and chi-square tests for dichotomous variables. An analysis plan will be constructed to account for the fact that some patients will have one study eye and some patients two study eyes and also for the stratification based on the presence/absence of unthickened retina at baseline.

For phase 2, the proportion of patients not requiring additional treatment at 12 months in whom DME recurs in each group will be determined and 95% confidence intervals constructed. The proportion in each group will be compared in an exploratory analysis. Patients who are considered to have 'failed' laser treatment at 12 months and receive intravitreal steroids will be evaluated with regard to the change in acuity and change in OCT that occurs. Additional analyses will replicate those listed for phase 1. A noted in chapter 1, all phase 2 results will be interpreted with caution.

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