Diabetic Retinopathy Clinical Research Network

Effect of Diabetes Education during Retinal Ophthalmology Visits on Diabetes Control

Version 1.0

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Chapter 1
INTRODUCTION

1.1 Background and Rationale

1.1.1 Metabolic Control and Diabetic Retinopathy

Complications of diabetic retinopathy cause between 12,000 to 24,000 new cases of blindness each year.[1] The prevalence of diabetic retinopathy in diabetic patients 40 years of age and older exceeds 40%, with 5% to 10% developing vision-threatening complications, including proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, or macular edema.[2] Recent projections estimate that the number of cases of diabetic retinopathy in the United States will triple from 5.5 million to 16 million by 2050.[3] It is well established that improved glycemic, blood pressure, and perhaps lipid control can reduce ocular complications from diabetes.

Results from the Early Treatment Diabetic Retinopathy Study (ETDRS) show that better glycemic control inhibits retinopathy progression among all age groups, type 1 and type 2 diabetes, and all stages of retinopathy.[4] The ETDRS also found that reducing elevated blood lipids can slow the progression of retinopathy.[4] The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that improved blood glucose control can reduce the risk of developing retinopathy in patients with type 2 diabetes.[5] The Diabetes Control and Complications Trial (DCCT) found that intensive therapy, aimed at keeping glycemic levels as close to normal range values as possible, reduced the risk of any retinopathy developing by 76% (95% confidence interval (CI)= 62 % to 85%) among patients with no retinopathy at baseline and slowed the progression of retinopathy by 54% (95% CI= 39% to 66%) among patients with mild retinopathy at baseline.[6] The benefits of intensive treatment were sustained for approximately 4 years after the period of intensive glycemic control with a 75% ($P<0.001$) risk reduction in the progression of retinopathy.[7]

The UKPDS also examined the effect of tight blood pressure control (<150/85 mmHg) on the risk of ocular complications.[8] After 9 years, patients assigned to tight blood pressure control had a 34% (99% CI= 11% to 50%; P=0.0004) reduction in retinopathy progression and a 47% (99% CI= 7% to 70%; P=0.004) reduced risk of visual acuity decline by 3 lines.[8]

Despite the resulting clear and substantial beneficial effects, achieving optimal systemic control and patient compliance are often elusive. A study examining the results from the 1999- 2000 National Health and Nutrition Examination Survey (NHANES) estimated that only 7.3% of adults with diabetes attained recommended goals of Hemoglobin A1c (HbA1c) level less than 7%, blood pressure less than 130/80 mm Hg, and total cholesterol level less than 200 mg/dL (5.18 mmol/L).[9] Another recent study found that only 4% of patients with diabetes reported meeting therapeutic goals for the major risk factors for diabetes complications.[10] Further efforts are needed to increase compliance in controlling these risk factors among individuals with diabetes.

1.1.2 Diabetes Education and Diabetes Management

A lack of patients' understanding of the role that HbA1c and blood pressure play in diabetes management may hinder patient compliance in achieving optimal systemic control. Several

studies suggest that glycemic control may not be well understood and that the concept of HbA1c testing is frequently misinterpreted or misunderstood by diabetic patients. Results from two studies show that approximately 24% of diabetic patients accurately recalled their last HbA1c value.[11, 12] However, knowledge of HbA1c alone was not associated with better diabetes self-management. [11-13] From these results we can infer that efforts to provide patients with information regarding their diabetes health must include educational and behavioral elements that motivate patients to more effectively manage their diabetes enabling them to achieve optimal systemic control.

Diabetes self-management education has the potential to increase patients' understanding of HbA1c, blood pressure, and lipid control.[14-16] Studies have found that diabetes education can be effective in promoting better self-management and more regular metabolic testing, resulting in a decrease in HbA1c levels to target levels.[14-17] One randomized, unmasked controlled trial examined the effect of a brief, office based educational intervention on patient knowledge of diabetic control factors within a tertiary eye care center.[18] The results suggested that brief statements about glycemic control from an ophthalmologist may impact patient understanding of diabetic control.[18] A study conducted by Lee et al demonstrated that a web-based patient oriented diabetic education management system was effective in helping patients control their glucose, HbA1c and total cholesterol levels.[15] Most studies examining the effects of diabetes education on diabetes control have been non-randomized studies conducted in a hospital setting or as part of an outpatient education program.[14-17] A randomized controlled trial is needed to determine if diabetes education in an ophthalmology office setting is effective.

1.1.3 Rationale for Diabetes Education During a Retina Examination

Although each patient with diabetes should be receiving diabetic education as part of their on-going routine medical care, it is likely that such education is delivered with different details and intensity. Motivating a patient with diabetes to become involved in his or her care is of primary importance in achieving better systemic control.

Ocular complications from diabetes remain the most common cause of blindness among American adults 20-74 years of age.[1] A recent survey reported that loss of vision is the most feared of all diabetic complications.[19] Thus, it is possible that an educational intervention at an ophthalmology office may have additional impact beyond the current standard of diabetes education at a primary care or diabetologist/endocrinologist office alone. This study will determine whether diabetes education in the ophthalmology office (which includes same-visit feedback of HbA1c levels, combined with standardized education regarding same-visit blood pressure, retinopathy status and overall diabetes education) can improve subsequent HbA1c as compared with current standard care in an ophthalmology office.

Materials used in this research setting must be applicable for use in ophthalmology practices`. Therefore, the materials and procedures for this study have been developed with the goal of easy translation to this audience.

1.2 Study Objective

The primary objective is to assess whether glycemic control (assessed with HbA1c measurement) in individuals with type 1 or type 2 diabetes can be improved with a point-of-care

measurement of HbA1c in the ophthalmologist's office combined with a personalized risk assessment for diabetic retinopathy and other complications of diabetes.

1.3 Synopsis of Protocol

A. Study Design

The study design is a randomized clinical trial in which investigators or sites will be randomized to provide either intervention (in the form of personalized diabetes education) or usual care to study participants.

B. Major Eligibility Criteria

1. Age ≥18 years
2. Diagnosis of diabetes mellitus (type 1 or type 2)
3. Patient is not eligible if patient has a known HbA1c (patient report or available records at time of enrollment) <7.5% within prior 6 months

C. Treatment Groups

Study participants will be assigned to either the intervention or the control group (see section D for details on study participant treatment group assignment).

1. Intervention Group
   The intervention will consist of the following at enrollment and at each follow-up visit (but no more frequently than once every 12 weeks):
   - Measurement of HbA1c in office with immediate feedback
   - Measurement of blood pressure with immediate feedback
   - Assessment of retinopathy risk with immediate feedback
   - Personalized risk assessment reports based on current HbA1c
   - Brief assessment of patient understanding of key issues with immediate feedback
   - Supplemental diabetes management educational materials (provided at baseline only)
   - Feedback to primary care provider
   - Email reminder to study participants with email access of individualized risk assessment findings

2. Control (Usual Care)

D. Treatment Group Allocation

Investigators or sites will be randomized to provide either intervention or usual care to study participants (see Chapter 2 for details on randomization). A study participant will be assigned to either the control or intervention group according to which treatment group the enrolling investigator is randomized.

E. Sample Size

The sample size is estimated to be at least 2000 study participants with baseline central laboratory measured HbA1c ≥6.0%. It is anticipated that enrollment will exceed 2000 participants to enroll 2000 participants with baseline HbA1c ≥6.0%. The study will include 50 cluster units, which are sites or investigators, depending on which unit is randomized (see section 8.1.3). Recruitment for each cluster unit (investigator or site) will end after enrollment of 40

study participants with a central laboratory measured HbA1c value ≥6.0%.

Approximately 40 sites are expected to participate. *Note: Centers that are currently measuring HbA1c or providing formal diabetes education of similar or greater intensity to the trial's intervention as part of usual care may not be eligible to participate.*

F. Duration of Follow Up

- Duration of follow-up is 24 months with primary outcome at 12 months.

G. Follow Up Visit Schedule

- All study participants will have follow-up visits at 12 months and 24 months at which time outcome assessments will be made.
- Additional visits will be conducted as needed for the study participant's eye condition.

H. Primary Outcome Measures

1. Mean change in HbA1c from baseline to 12 months in intervention versus control for study participants being seen for standard care more frequently than every 12 months.
2. Mean change in HbA1c from baseline to 12 months in intervention versus control for study participants being seen for standard care every 12 months.

Only study participants with a baseline central laboratory HbA1c value of ≥6.0% will be included in the primary analysis.

I. Secondary Outcome Measures:

1. Change in HbA1c at 3 months (includes only participants with routine eye care visits at 3 months) and change in HbA1c at 24 months
2. Diabetes care knowledge assessment at 12 months and 24 months
3. Body mass index (BMI) at 12 months and 24 months
4. Blood pressure at 12 months and 24 months

1.4 General Considerations

The study is being conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) 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.

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

Chapter 2
INVESTIGATOR RANDOMIZATION

2.1 Selection of Investigators/Clinical Sites for Participation

Approximately 40 DRCR.net sites will be selected to participate in this study. Both single investigator sites and multi-investigator sites will be eligible to participate. The study will include private practices and institutions which are representative of a diverse patient population in terms of race/ethnicity, level of education, and socioeconomic status.

Sites that routinely measure HbA1c in the office during the ophthalmology visit or routinely provide formal education in diabetes management of similar or greater intensity to the trial's intervention, as part of the ophthalmology visit, will not be eligible to participate.

Site selection criteria will include race/ethnicity distribution of patients at the site and study recruitment in prior DRCR.net studies.

2.2 Randomization

2.2.1 Randomization by Site

Sites with multiple investigators will be given the option to randomize the entire site as one unit (i.e. all investigators at the site will be randomized to either intervention or control) or to randomize their investigators separately. Sites with only one participating investigator or sites selecting to randomize by site will be randomly assigned (stratified by breakdown of site reported race/ethnicity distribution into the following 4 strata: (1) ≥15% Black/African American and ≥ 15% Hispanic or Latino, (2) ≥15% Hispanic or Latino (<15% Black/African American), (3) ≥15% Black/African American (< 15% Hispanic or Latino), and (4) other; with equal probability to 1 of the 2 groups.

2.2.2 Multi-Investigator Sites

Sites with two or more participating investigators may choose to be randomized by site or by investigator. For sites selecting to randomize by investigator with only 2 investigators, the investigators will be randomized in a 1:1 ratio, stratified by site. For sites selecting to randomize by investigator with more than 2 investigators, the site will divide the investigators into 2 groups and each of the 2 groups of investigators will be randomized in a 1:1 ratio, stratified by site.

2.2.3 Terminology

Throughout the remainder of the protocol, the term cluster unit will be used to refer to either a site, if the site is randomizing by site; an investigator if a site with 2 investigators is randomizing by investigator; or an investigator group if a sites with more than 2 investigators is randomizing by investigator.

Chapter 3 ELIGIBILITY AND ENROLLMENT PROCEDURES

3.1 Identifying Eligible Potential Study Participants and Obtaining Informed Consent

The study will include a minimum of 2000 study participants. Recruitment will continue until there are at least 2000 participants enrolled with baseline HbA1c $\geq$6.0%. Each cluster unit is required to enroll at least 22 participants scheduled to return for annual (12 months) standard care visits and 18 participants scheduled to return more frequently for standard care visits, for a total of 40 participants per cluster unit, with a baseline HbA1c $\geq$6.0%.

Potential eligibility will be assessed when patients present for routine-care examination. Sites will approach the first eligible individual seen during a clinic session and the study protocol will be discussed with the potential study participant by a study investigator and/or clinic coordinator. The consent form will be reviewed with the potential study participants and the potential study participant will be given time to review the written consent form and ask questions. If the first individual declines participation, the study protocol will be discussed with the next consecutive individual. The first enrolled participant must complete his/her visit before the next eligible individual can be enrolled. After the first participant completes the visit, the site must approach the next eligible individual as described above. The procedure for identification of potential study participants was defined in this manner in order to reduce potential selection bias. Sites will track the number of individuals who decline participation in the study. No identifying information will be recorded.

Prior to completing any study procedures or collecting any data that are not part of usual care, including measurement of HbA1c in the office, written informed consent will be obtained. The study participant will be given a copy of his or her signed consent forms. Consent forms will be customized based on the treatment group that the potential study participant will be assigned to.

3.2 Eligibility and Exclusion Criteria

3.2.1 Inclusion

Potential participants must meet all of the following inclusion criteria:

1. Age $\geq$18 years
2. Diagnosis of type 1 or type 2 diabetes mellitus
   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 American Diabetes Associate and/or World Health Organization criteria*
3. Routine care follow-up is yearly or more frequent
4. English or Spanish speaking
5. Able and willing to provide informed consent
6. Willing to complete 24 months of study follow up

3.2.2 Exclusion

A potential participant is not eligible if <u>any</u> of the following exclusion criteria are present:

1. Known HbA1c (patient report or available records at time of enrollment) <7.5% within prior 6 months
2. Active participation in any type of intervention study
3. Initiation of insulin treatment within 3 months from date of enrollment
4. Prior complete panretinal photocoagulation or prior diabetes-related vitrectomy in both eyes
5. Advanced visual acuity loss in both eyes which prohibits ability to read study materials (tested as needed with reading test using materials in appropriate size script)
6. Significant renal disease including use of erythropoietin (Procrit, Epogen, Eprex) or a history of chronic renal failure requiring dialysis or kidney transplant

3.3 Tracking Potential Study Participants Not Enrolled

Sites will track the number of individuals who decline participation in the study. No identifying information will be recorded.

Chapter 4
STUDY PROTOCOL

4.1 Baseline History and Testing

4.1.1 Baseline History

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

4.1.2 Baseline Testing Procedures

All study participants (control and intervention) will complete the baseline testing.

1. The following questionnaires will be completed (see Chapter 5):
   - Problem Areas in Diabetes (PAID) Questionnaire
   - Self-Care Inventory (SCI-2) Questionnaire

2. A blood sample obtained with a fingerstick and sent to the DRCR.net central laboratory at the University of Minnesota for measurement of HbA1c.
   - If a control group participant has a central-laboratory measured HbA1c >10.0%, a notification will be sent to both the primary diabetes care provider and to the participant advising that the HbA1c level was >10.0% (exact value will not be specified).
   - For intervention group participants, a second sample obtained with a fingerstick will be analyzed in-office using the study provided point-of-care instrument.

3. Measurement of blood pressure (using the study-provided blood pressure monitor)
   - The procedure for measurement of blood pressure is detailed in the Study Procedures Manual.

4. Ocular examination on both eyes including dilated fundus examination

5. Visual acuity should be obtained from the most recent (within 3 months) standard care assessment. If a recent visual acuity score is not available, standard care assessment (either with ETDRS or Snellen chart) should be used to obtain visual acuity.

6. Measurement of height and weight

4.2 Follow-up Visit Schedule and Procedures for Both Groups

4.2.1 Investigator Determination of Standard Care Visit Schedule

After completion of a routine care eye examination, the follow-up schedule will be determined by the investigator based on the routine care requirements for the study participant's eye condition. Follow-up visits may be on an annual basis (12 month schedule) or may be more frequent.

4.2.2 Outcome Visit Schedule

Outcome visits will occur for all study participants at:

- 12 Months (±4 weeks)

- 24 Months (±8 weeks)

4.2.3 Follow-up Testing Procedures

At 12 months and 24 months, all study participants will complete the following:

1. Blood sample obtained with a fingerstick for measurement of HbA1c sent to the DRCR.net central laboratory at the University of Minnesota
   - If a control group participant has a central-laboratory measured HbA1c >10.0%, a notification will be sent to both the primary diabetes care provider and to the participant advising that the HbA1c level was >10.0% (exact value will not be specified).
   - Study participants in both treatment groups who complete a visit between 9 and 17 weeks after the baseline visit will have the HbA1c central laboratory test repeated.
   - For intervention group study participants, a second sample obtained with a fingerstick will be analyzed in-office using the study provided point-of-care instrument.

2. Measurement of blood pressure (using the study provided blood pressure monitor)
   - The procedure for measurement of blood pressure is detailed in the Study Procedures Manual.

3. Measurement of height and weight

4. Ocular examination on both eyes including dilated fundus examination

5. The following questionnaires will be completed (see Chapter 5):
   - Problem Areas in Diabetes (PAID) Questionnaire
   - Self-Care Inventory (SCI-2) Questionnaire

4.3 Educational Intervention Schedule

4.3.1 In-office HbA1c Measurement

For intervention group study participants, a blood sample is obtained with a fingerstick at each educational intervention time point. The blood sample is analyzed in-office using the study provided point-of-care instrument.

4.3.2 Baseline Educational Intervention

Study participants in the intervention group will receive an educational intervention regarding diabetes management at the baseline visit. Chapter 6 details the educational intervention the study participant will receive at baseline.

4.3.3 Educational Intervention Procedures During Follow-up

Study participants will be seen as often as needed for routine care. In the intervention group, the educational intervention procedures, including in-office measurement of HbA1c, blood pressure and dilated fundus exam will be repeated at each routine care visit, but not more frequently than once every 12 weeks.

Chapter 5
QUESTIONNAIRES

5.1 Introduction

The questionnaires are completed by all study participants at baseline, 12 months and 24 months.

Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

5.2 Problem Areas in Diabetes (PAID) Questionnaire

The PAID Questionnaire is a validated measure of diabetes-specific emotional distress that was developed by the Joslin Diabetes Center, Boston.[20, 21] This self-administered questionnaire consists of 23 items that cover a range of emotional problems frequently reported in type 1 and type 2 diabetes. Each item is scored 0 to 4 ("Not a problem" to "Serious Problem"). This questionnaire will be completed by study participants at baseline, and again at the 12 month and 24 month outcome visits. Administration time is approximately 10 minutes.

5.3 Self-Care Inventory (SCI-2) Questionnaire

The SCI-2 Questionnaire is a validated measure used to assess whether or not a diabetes treatment care plan is being followed.[22-24] The SCI-2 was developed by Dr Annette LaGreca, and modified for use in adults by Dr Katie Weinger of the Joslin Diabetes Center, Boston. This self-administered questionnaire consists of 17 items that measure perceived adherence to diabetes self-care recommendations. Each item is scored 1 to 5 (“Never” to “Always”). This questionnaire will be completed by study participants at baseline, and again at the 12 month and 24 month outcome visits. Administration time is approximately 10 minutes.

Chapter 6
EDUCATIONAL INTERVENTION

6.1 Introduction

Study participants in the intervention group will receive a diabetes management educational intervention at baseline and at follow-up visits. For those on an annual follow-up schedule, educational intervention will take place at baseline and 12 months. For those whose standard care involves more frequent, than annual, visits the educational intervention will take place no more than once every 12 weeks.

The educational intervention will include:

- In-office measurement of HbA1c, blood pressure, and assessment of severity of retinopathy
- Personalized risk assessment reports providing risk of diabetic complications associated with the participant's current HbA1c value and target goals for improvement
- Supplemental diabetes management educational materials (provided at baseline only)
- Brief assessment of patient understanding of key issues with immediate feedback
- Feedback to primary care provider
- Email reminder to study participants with email access of individualized risk assessment findings

6.2 Personalized Risk Assessment Reports

A major component of the educational intervention is personalized feedback during the study visit with regard to current HbA1c, retinopathy level, and blood pressure. This feedback will highlight personalized risk for worsening retinopathy and kidney disease and the extent to which improved glycemic control may reduce these risks.

In order to minimize variability in time, approach, and depth of discussion among different investigators, a standardized scripted personalized report will be generated by the computer for each study participant. This scripted report will be read to the study participant by the investigator and the coordinator will review pertinent information. The scripted report will then be provided directly to the patient and sent to the primary provider.

Along with this scripted report, an easy to understand graph showing the risk of worsening retinopathy associated with the study participant's HbA1c will be provided. The study participant's current value along the curve will be indicated and the potential reductions in risk with improvement will be clearly evident. A few brief scripted sentences, similar to statements included in the scripted report, will be printed on the bottom of the graph for reference by the investigator. The investigator will answer questions as needed. At each follow-up visit a graph showing the participant's HbA1c values at each study visit, beginning with their initial study visit, will be provided to the participant.

The investigator or coordinator will ask the study participant to answer a simple set of questions at the conclusion of the scripted intervention to ensure the participants understanding of the provided information. If any questions are answered incorrectly, the investigator will review the

topic with the participant. This will provide an opportunity for the investigator to reinforce any components of the education that the participant may not have understood.

A copy of the reports will be sent to the primary care provider for their records. Study participants will be encouraged to discuss the information contained in the report with their primary care provider. If a participant does not have a primary care provider, a list of possible primary care providers will be provided to the participant.

6.3 Supplemental Diabetes Management Educational Materials

Study participants will also receive diabetes management educational brochures at the end of the baseline visit to take home for further review.

The brochures provided include:

- The American Diabetes Association, "What You Need to Know: Managing High Blood Pressure"
- The American Diabetes Association, "Diabetes Advisor: Checking Blood Glucose"
- National Institute of Diabetes and Digestive and Kidney Diseases, "Prevent Diabetes Problems: Keep Your Eyes Healthy"
- Joslin Diabetes Center, "On the Road to Living Well With Diabetes"

6.4 Email Reminder to Study Participants

After each visit which includes educational intervention, intervention group study participants will receive 2 emails (one email approximately a week after the visit and a second email approximately a month after the visit) reminding them of their individualized risk assessment findings. This communication will be through an authorization based email link which allows access to data through a secure website.

Chapter 7
MISCELLANEOUS CONSIDERATIONS

7.1 Risks

The collection of blood for measurement of HbA1c may cause some pain, discomfort and slight bruising.

As part of the study, study participants will complete psychosocial questionnaires which include questions about their private attitudes, feelings, and behavior related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

The study may include other risks that are unknown at this time.

7.2 Benefits

Study participants in the intervention group may benefit by having improvement in their diabetes control.

Study participants in the control group who have a central-laboratory measured HbA1c >10.0% at any time during the study will be notified, as will the study participant's primary care provider, as this is considered sufficiently high to warrant attention.

Study participants who do not have a regular source of non-ophthalmologic medical care will be provided with a list of physicians in their area.

7.3 Treatment of Macular Edema and Diabetic Retinopathy

Treatment of DME and diabetic retinopathy is at investigator discretion.

7.4 Diabetes Management

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

7.5 Study Participant Withdrawal and Losses to Follow-up

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

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

Study participants who withdraw will be asked to have a final closeout visit at which the testing described for the outcome visits should be performed if possible.

7.6 Discontinuation of Study

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

7.7 Confidentiality

For security purposes, study participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, Florida.

Laboratory specimens identified by the number assigned to the study participant will be sent to the central laboratory at the University of Minnesota.

7.8 Contact Information Provided to the Coordinating Center

The Coordinating Center will be provided with contact information for each study participant including the participant's email address. Permission to obtain such information will be included in the Informed Consent Form. The contact information will be maintained in a secure database and stored separately from the study data.

7.8.1 Correspondence with Primary Care Provider

A copy of the study participant's risk assessment reports will be sent to the primary care provider for their records.

Study participants in the control group who have a central-laboratory measured HbA1c >10.0% at any time during the study will be notified, as will the study participant's primary care provider.

7.8.2 Correspondence with Study Participant

After each visit that includes educational intervention, intervention group study participants will receive two emails reminding them of their individualized risk assessment findings. This communication will occur through an authorization based email link which allows access to data through a secure website.

Phone contact from the Coordinating Center will be made with study participants if necessary to facilitate the scheduling of follow-up visits in order to assist sites with study visit compliance.

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

7.9 Costs of Testing and Care

The study participant will not be responsible for the costs of any testing that is done for research purposes, including:

- In-office measurement of HbA1c (intervention group)
- Blood sample for DRCR.net central laboratory measurement of HbA1c
- Measurement of blood pressure, height and weight
- Educational intervention

The study participant will be responsible for testing that is performed as part of his or her usual care and not as part of a study visit including:

- Eye exam

7.10 Study Participant Reimbursement

For completed visits at baseline, 12 months, and 24 months study participants will receive a $25 Amazon.com gift card.

Additional travel expenses may be paid in select cases for study participants with higher expenses.

7.11 Adverse Events

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. Adverse event reporting will be limited to severe hypoglycemia as defined by DCCT criteria.[25] Severe hypoglycemia is any event requiring the assistance of another person, due to altered consciousness of the study participant, to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he or she was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Each principal investigator is responsible for informing his or her Institutional Review Board (IRB) of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

7.12 Data and Safety Monitoring Committee

A DSMC will approve the protocol, template informed consent form, and substantive amendments and will provide independent monitoring of adverse events. Cumulative adverse event data are semi-annually tabulated for review by the DSMC. Following each DSMC data review, a summary will be provided to IRBs.

Chapter 8
STATISTICAL METHODS

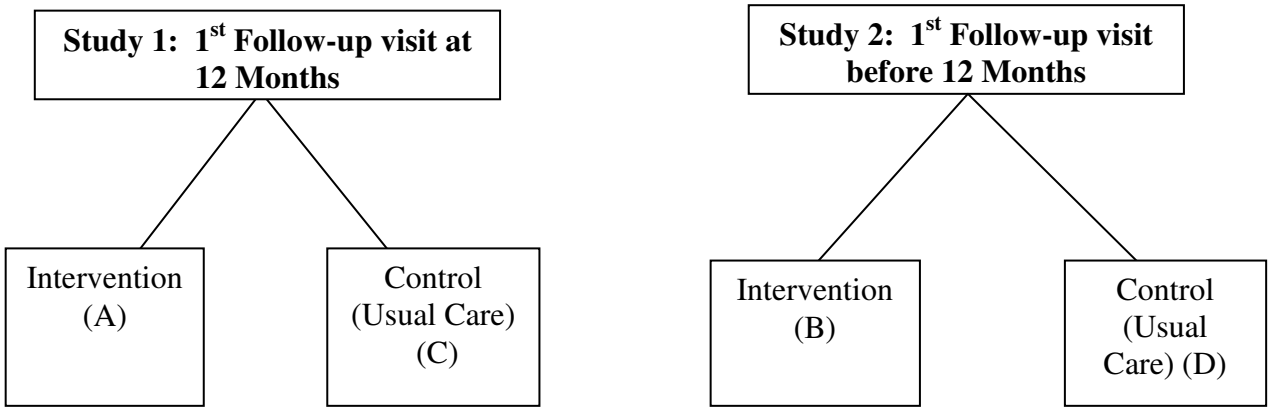
The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

The following are the 4 groups for analysis

A. Intervention – first standard care follow up visit at 12 months
B. Intervention – standard care follow up more frequently then every 12 months
C. Control – first standard care follow up visit at 12 months
D. Control – standard care follow up more frequently then every 12 months

Treatment Groups:

FIGURE 1



The primary analysis consists of a comparison of the mean change in HbA1c from baseline to 12 months for the following:

1. Intervention versus control for study participants being seen for standard care more frequently than every 12 months (Groups B vs. D in Figure 1 above)
2. Intervention versus control for study participants being seen for standard care every 12 months (Groups A vs. C in Figure 1 above)

Note: Only study participants with a baseline central laboratory HbA1c value of ≥6.0% will be included in the primary analysis.

8.1 Sample Size

The sample size goals below are for the subset of participants with a baseline HbA1c ≥6.0%. It is expected that very few participants will have an HbA1c level <6.0% and not have knowledge of a HbA1c test result from the past 6 months.

8.1.1 Control Group Projection

Data from 4 DRCR.net protocols that had baseline and 12 month HbA1c measurements (protocols A, B, D, E) on subjects with a baseline HbA1c at least 7% were used to estimate the control group distribution of the change in HbA1c from baseline to 12 months. (The primary analysis will include subjects with baseline HbA1c at least 6%, but the majority are expected to be at least 7%, and the standard deviation in this group is higher so the estimates will be more conservative). Based on the 651 subjects from 94 sites from these protocols in this cohort, the mean (± standard deviation) change in HbA1c from baseline to 12 months was a decrease of 0.4% ± 1.7%. The 95% CI on the standard deviation is (1.6%, 1.8%). A conservative estimate of 1.8% will be used.

Although the clusters will be based on a hybrid of randomization by site and by investigator, the sample size calculations will be based on a single cluster unit. Since the intracluster correlation coefficients (ICC) for sites and for investigators were both less than 0.01, a conservative estimate of 0.03 will be used.

8.1.2 Intervention Group Projections

It is expected that the intervention group will have a mean decrease 0.5% greater than the mean decrease in the control group for both comparisons.

Considering that the intervention will be standardized, the likelihood of a significant site effect is small.

8.1.3 Sample Size Estimation

Based on 90% power and alpha = 0.05 for a single 2 group comparison

ICC	Standard Deviation	Mean Difference Between Groups	Number of Clusters (per treatment group)	Number of Subjects per Cluster (per primary analysis comparison)
0.03	1.7%	0.3%	20	n/a
			25	137
			30	67
		0.5%	20	19
			25	13
			30	10
	1.8%	0.3%	20	n/a
			25	315
			30	100
		0.5%	20	22
			25	**16**
			30	12

The assumptions for both studies are as follows:

- Power = 90%
- Type 1 error rate = 0.05 (2-sided): The 2 primary analysis comparisons are considered distinct studies. Therefore a significance level of 0.05 will be used for each of these primary comparisons.

- Mean difference in 1 yr change in HbA1c levels between treatment groups = 0.5%
- Standard deviation of change= 1.8%
- ICC = 0.03

Based on these assumptions, the study will randomize 50 cluster units (sites or investigators) to the 2 treatment groups, i.e. 25 cluster units per treatment group. The required sample size for each cluster unit will be 16 participants per primary analysis comparison. To account for 10% loss to follow up (on a participant level), this will be increased to 18 participants per primary analysis comparison. To account for an additional 10% potential crossover of participants originally scheduled to return annually and instead return more frequently (i.e., Groups A and C crossover to Groups B and D in Figure 1 above) the sample size for Groups A and C will be increased to 22 participants expected to return annually for follow-up visits. This will yield a total of 40 participants per cluster unit between the 2 primary analysis comparisons, for an overall total of 2000 participants between both primary outcome comparisons.

8.2 Statistical Methods

8.2.1 Primary Analysis

HbA1c is the primary outcome variable. The primary outcome is the change in HbA1c from baseline to 12 months adjusted for the baseline HbA1c. Treatment group comparisons will be made using analysis of covariance (ANCOVA) to adjust for the baseline HbA1c, with generalized estimating equations (GEE) to adjust for the correlation within subjects of the same cluster.

The primary analysis will compare the following:

1. Mean change in HbA1c from baseline to 12 months controlling for baseline HbA1c in intervention versus control for study participants being seen for standard care more frequently than every 12 months (Groups B vs. D above)
2. Mean change in HbA1c from baseline to 12 months controlling for baseline HbA1c in intervention versus control for study participants being seen for standard care every 12 months (Groups A vs. C above)

These 2 primary comparisons are considered distinct studies. Therefore a significance level of 0.05 will be used for each of these primary comparisons.

In addition, mean change in HbA1c in study participants in the control and intervention group returning for a routine visit at 9 to 17 weeks will also be compared with each other to assess an initial effect.

The primary analysis will be an intent-to-treat analysis with study participants analyzed in the group to which assigned (intervention or control) regardless of how much education they actually received. However, regardless of what visit schedule the study participant was projected to be on, the participant will be analyzed in the primary analysis comparison group based on the actual number of completed follow-up visits.

Only available data at each visit will be used for the primary analysis. Sensitivity analyses will be conducted (1) using Rubin's multiple imputation technique and (2) setting all non-completers to have a mean change of 0. If these sensitivity analyses yield the same results as the primary analysis, they will be used to provide supportive evidence of the intervention. If the results of the methods differ from the primary analysis, exploratory analyses will be performed to evaluate the factors that have contributed to the differences.

The primary outcome completion rate will be calculated in all groups. Analysis will be performed on the completers and non-completers to confirm that there were no major differences in key baseline factors (e.g. HbA1c, diabetes type, diabetic retinopathy level, level of education or ethnicity/race) between treatment groups. Analyses on completers and non-completers will be done both by pooling the treatment groups and separately within the treatment groups.

Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in regression models by including baseline covariates that are associated with the outcome and are imbalanced between groups at baseline. There are no data to suggest that the treatment effect will vary by gender or race/ethnicity. However, both of these factors will be evaluated in exploratory analyses.

Pre-planned subgroup analyses will be described in the detailed Statistical Analysis Plan and include stratification by baseline HbA1c, age, diabetes type, retinopathy severity, level of education, and history of prior DME treatment.

8.2.2 Secondary Analyses

The primary analysis will be repeated for the 24 months data and the 3 month data for participant with a visit between 9-17 weeks. Additional analyses will be conducted on HbA1c to assess for consistency with the primary analysis. These will be conducted on the 12 month and 24 month data. The additional analysis will include the following:

- Proportion of study participants with HbA1c < 7.0%
- Proportion of study participants with HbA1c >10%
- Proportion of study participants with a relative decrease in HbA1c of at least 10% (outcome used in DCCT which translates into a 40% decreased risk of retinopathy progression for a 10% decrease in HbA1c)
- Proportion of study participants with a decrease in HbA1c of $\geq$0.5%
- Proportion of study participants with an increase in HbA1c $\geq$0.5%
- Mean change in blood pressure (see section 8.2.3 below))
- Mean change in body mass index
- Diabetes care knowledge assessment at 12 months and 24 months

For the above binary outcomes, logistic regression will be used adjusting for baseline HbA1c level with GEE to adjust for the correlation within subjects of the same cluster.

8.2.3 Blood Pressure Assessment

For analyses, systolic and diastolic blood pressure will be converted to an overall mean blood pressure according to the following calculation: diastolic blood pressure + 1/3 (systolic blood pressure – diastolic blood pressure). Blood pressure will be analyzed as the change in the weighted mean blood pressure from baseline to 12 months adjusted for the baseline weighted mean blood pressure. Treatment group comparisons will be made using ANCOVA to adjust for the baseline blood pressure, with GEE to adjust for the correlation within subjects of the same cluster.

8.2.4 Study Participant Assessments

At baseline and at annual visits, study participants in all treatment groups will complete self-assessment questionnaires in order to assess perception of emotional problems frequently reported in type 1 and type 2 diabetes and to measure perceived adherence to diabetes self-care recommendations. At the annual visits, summary statistics will be presented on the responses as appropriate to the distribution and the treatment groups will be compared controlling for baseline responses.

8.2.5 Subgroup Analysis

Study participants will be classified based on the frequency of visits to the retina practice. In general study participants will be classified as returning monthly, quarterly, semi-annually, or annually. Analyses mimicking the primary analysis will be performed in these subgroups: (1) within treatment groups to determine if there is an effect on HbA1c based on the frequency of office visits and (2) across treatment groups to assess if there is an interaction with the frequency of office visits and the treatment group. A formal adjustment for multiple comparisons will not be made.

Additional subgroup analyses will replicate the primary analyses in the following subgroups based on baseline measurements:

- HbA1c ≥7.5%
- Mean blood pressure ≥ 97 (equivalent to 130/80)
- Body mass index: underweight (<18.5), normal (BMI 18.5-24.9), overweight (BMI 25-29.9), obese (BMI ≥ 30)

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