Origin and Design of the Kroc Collaborative Study

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SUMMARY

Although the benefits of metabolic intervention on the microvascular complications of diabetes mellitus remain unproven, it is generally assumed though not proven that prognosis in terms of blindness and renal failure will reflect the long-term glycemic response to therapy. Treatment goals however remain poorly defined. Costs and hazards of achieving near-normoglycemia in insulin-dependent diabetes mellitus (IDDM) are major. A multicenter trial was proposed to test the hypothesis that in IDDM two levels of mean glycemia, sufficiently separated to examine the control/complications relationship, could be maintained by the six collaborating centers, using randomized patient allocation to conventional insulin therapy (CIT) and continuous subcutaneous insulin infusion (CSII) as the alternative treatment modalities. Methods of maintaining and monitoring metabolic control and of assessing renal and retinal responses were to be applied, evaluated, and possibly improved. All clinics shared a common experimental protocol, which received ethical approval at each treatment center. Retinal assessment facilities were provided by the Fundus Photograph Reading Center at the University of Wisconsin in Madison, and at the Diabetic Retinopathy Department, Royal Postgraduate Medical School, Hammersmith, United Kingdom. The Central Biochemistry Laboratory was at the University of Newcastle, United Kingdom. Collaborators agreed on policy for recruitment, baseline assessment, and randomization of patients with IDDM, complicated by early microvascular disease. CIT took the form of the unchanged prestudy regimen; glycemic goals were set for CSII and their achievement based on inpatient and outpatient sampling of plasma glucose. Glycosylated hemoglobin was measured, retinal abnormalities recorded photographically, and urinary albumin excretion quantitated at baseline, 4, and 8 mo in all patients. As a prelude to the larger multicenter trial required to resolve definitively the question of the costs and benefits of intensified treatment of IDDM, The Kroc Collaborative Study was designed as a test of the feasibility of using currently available methodologies, of meeting the logistic problems of concerted clinical action in multiple centers, and the use of central assessments and of the capacity to sustain the operation for long enough to make a long-term clinical trial of treatment and prevention of the microvascular complications a practical possibility. DIABETES 1985; 34 (Suppl. 3):5–12.

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Convincing experimental demonstration of the effect of diabetic control on microangiopathy in humans is lacking. The case for such an effect has been argued with great force,[1] but it rests heavily on uncontrolled clinical observations that do not distinguish between the variable severity of the diabetic state itself, the effectiveness of the treatment it receives, and the interaction between the two. Animal evidence, although valuable as models of the human disease, cannot be directly transposed. Retinopathic blindness[2] and nephropathic renal failure,[3] prime concerns in the human diabetic, have never been reproduced experimentally in animal models. The microvascular morphologic responses to diabetes in animals closely resemble but are not identical to those of human diabetic microangiopathy.

The proposition that "improved diabetic control" reduces the risk of complications is generally accepted as a guide to therapy by those charged with the care of diabetic patients.[4–7] What is less widely agreed is the degree of improvement that is necessary and the amount of time and trouble that it is worth investing in obtaining it. New approaches to treatment have made quite remarkable degrees of glycemic correction feasible and the past decade has seen efforts to use them to achieve improved blood glucose control vigorously implemented in many diabetes centers; but their application has spread to an unknown extent into the "therapeutic hinterland" where the great majority of diabetic patients receive their

care. The new goals of "tight control" demand much more time, effort, and expenditure in the care of diabetes, both of the medical services and of the patient. As hyperglycemia is ever more tightly controlled, the person with diabetes inevitably incurs an increased risk of hypoglycemia, and must accept, adapt, and learn to counter this hazard.

Four objectives were defined in the "core protocol" of The Kroc Collaborative Study and were accepted by all collaborating centers:

(1) To test the capacity of the participating centers to achieve and maintain target levels of near-normoglycemia using continuous subcutaneous insulin infusion (CSII) in patients with insulin-dependent diabetes mellitus (IDDM). The glycemia achieved by CSII was to be compared with that achieved with conventional injection therapy (CIT).

(2) To evaluate the effect of maintenance of different levels of glycemia as a means of testing the relationship of diabetic retinopathy and nephropathy to diabetic control.

(3) To examine nonglycemic aspects of metabolic control and their possible relationship to diabetic microvascular disease.

(4) To develop and refine methods to assess progression and regression of microvascular disease with particular reference to changes in microaneurysm counts and areas of nonperfusion of the retina.

In addition, individual centers were permitted to undertake additional "noncore" studies on their trial patients, which were deemed by the whole collaborative group not to affect the primary purpose of the project. Areas of interest included the assessment of "tight control" on various metabolic/hormonal variables and the application of additional organ function tests (e.g., nerve conduction studies, vitreous fluorophotometry).

Approval of the protocol and consent forms was obtained from the ethical review body of each institution before recruitment. Early in the recruitment period, each patient volunteer received a full explanation and opportunity for discussion of the objectives and methods of the study, and signed the consent form.

STUDY STRUCTURE AND ORGANIZATION

The centers. In general, each clinical group (the members of which are listed on pages 3 and 4 of this supplement) formed both a patient treatment team and a methodologic resource group for the entire study. These comprised:

(1) The University of Chicago, Department of Medicine, Section of Endocrinology, Chicago, Illinois, which was responsible for the C-peptide assays.

(2) Guy's Hospital Medical School, Department of Medicine, Unit for Metabolic Medicine, London, United Kingdom, which was responsible for the urinary albumin assays.

(3) Royal Postgraduate Medical School, Hammersmith Hospital, Department of Medicine, London, United Kingdom, which was responsible for the interpretation of retinal fluorescein angiograms.

(4) Mayo Clinic, Department of Medicine, Rochester, Minnesota.

(5) University of Western Ontario, London, Ontario, Canada, which functioned as the study secretariat.

(6) Yale University, New Haven, Connecticut, took responsibility for data management and analysis.

A seventh clinical center, Steno Memorial Hospital, Gentofte, Copenhagen, Denmark, took part in the preliminary planning of the study but withdrew at an early stage to pursue an independent trial based on a similar protocol (see pages 74–79).

In addition, the laboratory facilities at the Royal Victoria Infirmary, Newcastle Upon Tyne, United Kingdom, were utilized as a central biochemistry laboratory. As the study progressed, arrangements were made for the grading of retinal color photographs at the Fundus Photograph Reading Center, University of Wisconsin, Madison, Wisconsin, and for the processing of data at the Biostatistics Research Center, Farmington, Connecticut. Yale University, New Haven, Connecticut, took responsibility for data analysis (Data Collation Center).

Study group organization and communications. Because of the small number of centers participating, it was felt unnecessary initially to specify a coordinating center. Representatives of all participating institutions met from time to time during the planning and the subsequent treatment phase of the study. Details of the grant support were worked out with the director of the grants program of the Kroc Foundation (Walter F. Garey, Ph.D.), and were supported by progress reviews made at intervals during the course of the trial. Funding essentially covered materials, costs, and the substantial expense of travel to meetings. Centers provided clinical and nursing personnel from their own staff, but a fluorescein photograph research fellow received support as did the special costs of data compilation and analysis at New Haven. All participating centers were recognized and had variable experience in long-term CSII in the treatment of IDDM. Equipment (insulin pumps, meters) was to be provided from local sources.

PATIENT RECRUITMENT AND ELIGIBILITY

During the planning phase, it was recognized that patients for the study would be recruited from different sources, reflecting local patterns of health care. Patients were recruited by reference to clinic registers and from local publicity about the study among practitioners and patients. General and ophthalmologic eligibility acceptance criteria were applied locally in each center by a diabetologist (using an Initial Medical Assessment Form, Appendix 1) and by an ophthalmologist (using an Initial Eye Assessment Form, Appendix 2). An initial trial period of 8 mo was defined.

The general inclusion criteria were: (1) willingness to participate after a full discussion of the study; (2) age between 14 and 60 yr; (3) weight <130% of the upper limit of the range of desirable body weight according to height (Metropolitan Life Insurance Tables, 1959); (4) diabetes mellitus with a history of ketonuria, age of onset ≤35 yr, and of <30-yr duration; and (5) treatment with ≥15, ≤120 U of insulin daily for at least 2 yr before recruitment. The number of daily injections was not specified.

The general exclusion criteria were: (1) a confirmed sitting systolic blood pressure of ≥145 mm Hg; (2) urinary protein excretion of >1 g/day; (3) definite evidence of ischemic heart disease according to local criteria; (4) unstable diabetes (defined as three or more episodes of ketoacidosis in the preceding year); (5) pregnancy or lactation; (6) the taking of continuous medication (except for an oral contraceptive pill

or thyroid replacement); (7) the presence of any other condition which, in the opinion of the investigators, might interfere with the conduct of the trial; and (8) the demonstration of significant residual endogenous insulin secretory capacity, defined as a plasma C-peptide concentration of ≥0.1 pmol/ml in the postabsorptive state, and 6 min after the intravenous injection of 1 mg glucagon (see pages 31–36).

The ophthalmologic examination for eligibility included best corrected visual acuity, slit lamp assessment with intraocular pressure determination and fundoscopy with indirect ophthalmoscopy, direct ophthalmoscopy, and biomicroscopy. Best corrected visual acuity was measured using standard Early Treatment Diabetic Retinopathy Study (ETDRS) Snellen refraction charts supplied to each center. To document the retinal status, 30° nonsimultaneous stereoscopic fundus photographs were taken of eight standard fields of each eye according to the ETDRS protocol,[11] and fluorescein angiography was performed by a standardized technique (see pages 56–60).

Ophthalmologic inclusion criteria were formulated in accordance with the ETDRS classification, supplemented by a category designated PB (see pages 13–16 and 42–49) to secure a group of trial subjects, all of whom had at least one eye showing minimal diabetic retinopathy (i.e., two or more microaneurysms), but whose retinopathy fell short of the more severe grades, broadly described as severe preproliferative retinopathy or more, in both eyes. Fulfilling these criteria was based on the results of the initial standardized ophthalmologic examination and the local assessment of the fluoroangiograms. The initial series of color stereoscopic pair photographs was reviewed later and, in a few cases, proved on grading and analysis to depart from the inclusion criteria (no retinopathy observable in two patients, bilateral peripheral new vessels in one patient, see pages 50–55).

Baseline studies. Pretreatment characterization of subjects accepted into the trial comprised the following data, obtained during a scheduled hospital admission: a 24-h, 11-time point venous plasma glucose profile with samples taken before and 90 min after main meals, before the bedtime snack, and twice-hourly from midnight to 6 a.m. (measured at both local and central laboratories); a 24-h urine collection to measure glucose and albumin excretion rates and a mid-stream sample for bacterial culture; a postabsorptive serum sample for central laboratory estimation of triglycerides, cholesterol; a blood sample for glycosylated hemoglobin (HbA_1) estimated by local techniques and by the central laboratory. The results of the ophthalmologic examination and C-peptide determinations during eligibility screening constituted the baseline (0 mo) data for subjects accepted into the trial.

RANDOMIZATION

At each center, as a successive pair of subjects was admitted to the trial, the name of each member was written on the outside of one of a previously supplied pair of sealed envelopes that contained a card on which was written "CSII" or "CIT." The envelopes were presented to the patients and opened together with an investigator present. It had been agreed that any patient refusing the assignment would become ineligible for the study, while the other patient would be retained unpaired in the assigned treatment group. In the event, this occurred on only two occasions (see pages 13–16). Randomization was planned to continue until there were at least six paired subjects per center in each treatment group.

TREATMENT PROCEDURES

MANAGEMENT STRATEGIES AND THERAPEUTIC OBJECTIVES

CIT group. Treatment was continued along the lines prevailing at each individual center, avoiding any action prejudicial to the usual standards of diabetes care. Glycemic goals were not specified. Each center used customary practices to avoid extremes of hyperglycemia, ketosis, and symptomatic hypoglycemia, maintaining previous routines of insulin injection and self-monitoring, usually with semiquantitative urine tests. Self-monitoring of blood glucose (SMBG) was not initiated unless clinically indicated but if established was continued as before. Insulin, syringes, and urine testing materials were supplied by the centers.

CSII group. After admission for baseline assessment and randomization, patients assigned to CSII were again admitted to hospital for institution of therapy, including instruction in the use of insulin pumps and in the techniques of SMBG, using either Dextrostix with an Eyetone or Dextrometer meter (Ames Division, Miles Laboratories Inc., Elkhart, Indiana) or visually read Chemstrip bG (Bio-Dynamics/BMC, Indianapolis, Indiana). After initial instruction and metabolic stabilization in hospital, patients were discharged, and followed closely by the physician and nurse-coordinator, with adjustments to the dietary and insulin infusion program according to frequent SMBG determinations. Glycemic goals in the CSII group, as determined by SMBG (the accuracy of which was checked against venous plasma glucose levels), were overnight fasting and before main meals 55–115 mg/dl (3–6.4 mmol/L) and 90 min postprandial <160 mg/dl (<9 mmol/L). Semiquantitative urine tests for glucose and ketones were performed if so directed by local clinical personnel. During the 8-mo course of the study, at least four SMBG samples on 2 days per week were requested, distributed between preprandial and 90 min postprandial time points.

STUDY MANAGEMENT

All treated patients were seen at regularly scheduled outpatient visits at 2 and 6 mo, and during brief admissions at 4 and 8 mo. The CSII group was also seen at intervening monthly intervals (1st, 3rd, 5th, and 7th mo). All patients had free access to the nurse-coordinator and to a study physician between visits, but frequent communication with the CSII patients was particularly emphasized and was frequently initiated by clinic personnel. Measurement of HbA_1 by the local and central laboratory was performed at 2, 4, 6, and 8 mo.

Hospital assessments. The 4- and 8-mo assessments were similar to those at baseline and included plasma C-peptide concentrations estimated before and 6 min after intravenous glucagon injection. A questionnaire dealing with subjective responses to therapy was applied at the 4th and 8th mo (see pages 37–41). The baseline (0 mo, eligibility) ophthalmologic examination was repeated at 4 and 8 mo and included fluorescein angiography, although at 4 mo only macular color photographs were taken (standard views 1 and 2).

Outpatient assessments. A clinical event questionnaire was completed at months 2 and 6 for the CIT group and monthly

for the 8-mo duration of the study in the CSII group (see pages 37–41). Current dietary practice, insulin injection dosage in the case of CIT patients, and insulin infusion rates and bolus dosages in the case of CSII patients were noted. Treatment adjustments were to be made on the basis of urine testing data or SMBG data in the CIT and CSII treatment groups, respectively. Patients brought or mailed to the clinic at monthly intervals a seven-sample set of self-collected capillary blood samples obtained in pretreated, fluoride-heparin tubes (#446/13, Walter Sarstedt Inc., Princeton, New Jersey).[14] These samples were taken before and 90 min after the main meals, and before the bedtime snack. Plasma glucose concentrations in these samples were also measured in the local laboratories.

Special visits. Provision was made for unscheduled clinic visits or hospital admissions pertaining to unforseen clinical events (e.g., ketoacidosis or severe hypoglycemia), or technical problems related to CSII (e.g., change in type of insulin pump). Local definitions of diabetic ketoacidosis and hypoglycemic episodes prevailed, although some attempt at uniform recording was made.

Patient dropouts. Patients refusing to continue in the trial, becoming pregnant, or developing major medical or psychiatric illness were considered "dropouts," and the data management center was so informed.

LABORATORY METHODS AND DATA PROCESSING

Biochemistry. The proposed roles intended for the local laboratories at clinical centers and for the central laboratory are outlined on pages 17–21. The Manual of Operations provided details of the methods for sample acquisition, labelling, processing, freezing, packing, and dispatching to the laboratory. A mechanism for quality control of the local plasma glucose assays was proposed and administered by the central laboratory. Local standardization of plasma glucose and HbA_1 estimations, although desirable, was considered impracticable since most centers were committed to different methods. Although central measurement of HbA_1 and glucose were originally considered to be the principal analytic variables, in the event the presentation and transport of the former proved to be inadequate and it was necessary to resort to the use of local estimations (see pages 22–26).

Data management. At the Data Collation Center (Yale), arrangements were made for the utilization of the resources of the Biostatistics Research Center, Farmington, Connecticut. Initial assessments, hospital admissions, scheduled and unscheduled clinic visits, and patient dropouts were entered onto prepared forms for transmission to Yale for review, and for the retrieval of missing data from individual centers. Telephone communication proved a useful medium for rapid requests and queries of this sort.

DISCUSSION

The purpose of the clinical trial, to examine the feasibility of obtaining objective experimental evidence in humans on the relationship between the control of diabetes mellitus and the microangiopathic complications, appears to require little justification. However, Tchobroutsky et al.[15] have argued that such trials can have little value. If they are sufficiently rigorously planned to explain pathogenic mechanisms underlying differences in control they would bear little relation to "real life" treatment of diabetic patients. If they are simply empirical comparisons between different complex clinical treatment regimens it is hardly possible, they argue, to identify which component of the treatment might have been responsible for differences in microangiopathic response, making it difficult to evaluate the balance of costs and benefits. In any case, they feel that the evidence of benefit is now so strong that physicians are clinically bound to strive for near-normoglycemia in all suitable insulin-dependent patients. To await the results of trials suggests that doubt remains and may needlessly condemn another generation of patients to blindness and renal failure. While this argument has theoretical strength, it fails to recognize the reservations felt by many physicians about submitting their patients (and themselves) to the considerable extra effort, expense, and perhaps dangers of striving for near-normoglycemia.[16] Many, probably most, physicians will reset their treatment goals nearer physiologic levels only if clear experimental demonstration of some advantage in man convinces them that it is worthwhile. It was our purpose to start to provide this evidence.

A clinical trial of improved control on diabetic angiopathy may be based either on its effects on the first appearance of abnormalities in persons currently unaffected, that is, on the *genesis* of microangiopathy—alternatively such a trial can be aimed at showing an effect on its *evolution,* taking as its experimental subjects patients already demonstrating some abnormality (e.g., retinopathy). In the latter case, the degree of abnormality must not be so great as to make an effect of treatment on it unlikely, nor so slight that an effect might be difficult to demonstrate. We chose the latter case as giving us the better opportunity to test our existing analytic methods for retinal and renal responses and in the hope that we might, even in the short period of the feasibility study, be fortunate enough to demonstrate a therapeutic effect. Such scanty prior evidence as there was suggested that this might be the case, although quantitative knowledge of the natural history of retinopathy at the time was inadequate to make any but the most insecure calculations of the liklihood of showing a meaningful effect. Of this we were well aware and so formulated the prime purpose of the study as a test of feasibility. Factors other than glycemic control such as cigarette smoking and hypertension, suspected to influence the course of diabetic microangiopathy, were either excluded by recruitment procedures (e.g., hypertension) or documented for later analysis (e.g., tobacco smoking).

The main measure of efficacy of the experimental treatment was glycemia or some function of it. Three indices were selected: the home glycemic profile (collected by the patient but estimated in the laboratory), the 24-h hospital glycemic profile, and the 4- or 8-weekly estimates of HbA_1. Results of self-estimated (monitored) samples were not used as analytic variables for the study although they were employed in optimizing therapy.

The other biochemical variables measured (e.g., plasma lipids) were included as additional indicators of the metabolic response to treatment and were neither major analytic variables nor study endpoints.

There was some debate as to whether the study should also include a group subjected to "optimized" conventional control. It was decided that this would weaken the study more

by reducing treatment group numbers and strengthen it by widening its practical applications.

CSII was chosen as the "tight control" treatment method because of its proven success in achieving long-term glycemic near-normalization.[17–19] It appeared to offer the best-documented method of providing two experimental groups with clearly separated levels of glycemic control, the lower of which approached normoglycemia. It was the intention of the protocol to alter levels of control as little as possible in the CIT group.

The expectation that quantitative analysis of fluorescein angiograms (and particularly the microaneurysm count) would be developed as the primary study outcome variable was not, in the event, sustained. Its place was taken by the analysis of the stereoscopic paired color photographic retinal surveys, methods for which were approaching completion in Madison, Wisconsin. The validation of microalbuminuria as a predictor of clinical diabetic nephropathy[20–22] gave particular point to the inclusion of urinary albumin excretion rates as an outcome variable. A fuller consideration of these analytic variables and study outcomes is to be found on pages 50–73.

CONCLUSIONS

Clear demonstration of clinically significant benefit from improved metabolic correction on diabetic microangiopathy in man may emerge from uncontrolled, unplanned, widespread improvement in the norms of diabetic control; at present there is no indication that this is occurring. Reliable demonstration of benefit is likely to require the design, implementation, and analysis of a large-scale clinical trial conducted in representative diabetic patients over a substantial period of time. The Kroc Collaborative study was initiated to see whether such a trial was even feasible. Was it clinically possible to assign patients randomly to two levels of treatment? Would the glycemic responses differ significantly and sufficiently to make an answer to the question approachable? Even if they did, were there suitable methods in place, sensitive and robust enough to give a positive answer or to stand up to criticism were the answer negative? Whether the study succeeded in answering all or any of these questions, wholly or in part, must be left to the judgment of those considering the evidence of the succeeding sections.

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APPENDIX 1: INITIAL MEDICAL ASSESSMENT FORM USED IN SCREENING PATIENTS FOR GENERAL MEDICAL ELIGIBILITY

Patient's Name _____ Date of Birth _____
Last First Init (mo day yr)

Sex Male _____ Female _____

Address _____ Center _____

_____

Step 1: Fill Out Questionnaire		Exclusions
1. Willing to participate and be randomized	Yes _____ No _____	No excludes
2. History of ketosis or DKA	Yes _____ No _____	No excludes
3. Age now	_____ years	<14 or >60
4. Age at diagnosis	_____ years	>35

5. Duration of diabetes	_____ years	≥30
6. Total daily insulin dosage	_____ U/24 h	<15 or >120
7. Other major medical diseases	Yes ____ No ____	Yes excludes
If yes, specify: _____		
8. Major medications (other than insulin)	Yes ____ No ____	All except BCP's or thyroid
List major medications: _____		
9. Number of hospitalizations for DKA in past year _____		≥3
10. History of angina/infarct	Yes ____ No ____	Yes excludes
11. Pregnant/lactating	Yes ____ No ____	Yes excludes
12. Cigarette smoker	Yes ____ No ____	

Step 2: If no exclusions, then perform physical examination

13. Height	_____ cm	
14. Weight	_____ kg	
15. Body frame: Small _____	Medium _____ Large _____	
16. % Ideal weight	_____ %	>130 excludes
17. Sitting BP: Systolic	_____ (mm Hg)	≥145 systolic excludes
Diastolic (muffles)	_____ (mm Hg)	
Diastolic (disappears)	_____ (mm Hg)	
18. Crude visual acuity (corrected)	Normal ____ Impaired ____	Impaired excl.
19. Neurologic findings:		
a) Vibratory sense (feet)	Present _____ Absent _____	Neuropathy does *not* exclude
b) Ankle jerk reflex	Present _____ Absent _____	
c) Clin. autonomic neuro	Present _____ Absent _____	
20. Record below other abnormal physical findings.		
Check here if other excluding physical findings discovered ____		Check excludes

Step 3: If no exclusions, then

21. Patient gives written informed consent	Yes ____ No ____	No excludes
22. Check if: Blood obtained for HbA_1	local ____ central ____	
—Serum creatinine	____	
—Fasting C-peptide	____	
—Postglucagon (6 min) C-peptide	____	
—C-peptide sent to Chicago	____	

23. Check if scheduled:
ECG _____ Eye exam _____ 24-H urine collec. _____

Step 4: Record initial laboratory data below and complete eye evaluation sheet

24. Serum creatinine	_____ mg/dl	abnormal (local)
25. Basal C-peptide	_____ pmol/ml	≥0.1 pmol/ml
26. Postglucagon C-peptide	_____ pmol/ml	≥0.1 pmol/ml
HbA_1 (local lab)	_____ %	

27. ECG abnormality Yes ____ No ____

    If yes, specify: _____ abnormal Q/ST excl.

28. Urine protein _____ mg/24 h >1.0 g/24 h excl.

29. Meets eye criteria (retinal photos) Yes ____ No ____

Step 5: If eligible, then

30. Assign ID Number _____
31. Forward this form to Data Center
32. Schedule initial hospital admission:

    Tentative date of admission _____
    (month day year)

APPENDIX 2: INITIAL EYE ASSESSMENT FORM USED IN SCREENING PATIENTS FOR OPHTHALMOLOGIC ELIGIBILITY

Patient's name _____ Date of exam _____ (mo day yr)

ID Number _____ Examiner _____

Center: _____

	Right	Left
1. Refraction:		
2. Best corrected vision:		
ETDRS chart 1 or 2		
3. Corneal opacity? (yes/no)		
If yes, does it interfere with examination? (yes/no)		
4. Iris neovascularization? (yes/no)		
5. Cataract? (yes/no)		
If yes, does it interfere with examination? (yes/no)		
6. Aphakia? (yes/no)		
7. Angle neovascularization? (yes/no)		
8. Intraocular pressure (mm Hg)		
9. Vitreous opacity? (yes/no)		
If yes, does it interfere with examination? (yes/no)		
10. Optic disc findings (yes/no)		
Normal		
Neovascularization		
Atrophy		
Other (specify)		
11. Retinal findings (yes/no)		
Normal		
Neovascularization		
Hard exudates		
Cotton-wool spots		
Hemorrhages/microaneurysms		
IRMA's		

12. Macular edema? (check)

Definite	_____ /	_____
Absent	_____ /	_____
Uncertain	_____ /	_____

13. Estimated grade of retinopathy based on fundoscopy and stereo photos (ETDRS + B) _____ / _____

If one or both eyes meet inclusion criteria and there are no exclusions, the patient is formally admitted into the study. Please forward this form with the initial medical assessment form to the Data Center.