

P R O T O C O L

(Full-Scale Clinical Trial – Phase III)

for the

Diabetes Control and Complications Trial

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TABLE OF CONTENTS

ABBREVIATIONS USED	I
SUMMARY	II
1. INTRODUCTION	1
1.1 SCOPE AND IMPACT OF DIABETES.....	1
1.2 RATIONALE FOR THE DCCT STUDY QUESTION	2
1.3 BACKGROUND	3
1.4 FUTURE DIRECTIONS	5
2. OBJECTIVES AND DESIGN	7
2.1 OBJECTIVES.....	7
2.2 DESIGN	8
3. SAMPLE SIZE.....	11
3.1 INTRODUCTION.....	11
3.2 NATURAL HISTORY OF RETINOPATHY.....	11
3.3 STUDY DURATION AND SAMPLE SIZE	12
3.4 POWER.....	13
3.5 INTERIM ASSESSMENTS.....	15
3.6 SUMMARY.....	15
4. SUBJECT SELECTION AND RECRUITMENT	19
4.1 INTRODUCTION.....	19
4.2 ELIGIBILITY CRITERIA	19
4.2.1 Eligibility Criteria Applicable to All Subjects	19
4.2.2 For Subjects Without Retinopathy	19
4.2.3 For Subjects With Minimal Background Retinopathy	20
4.3 EXCLUSION CRITERIA.....	20
4.3.1 Exclusion Criteria Applicable to All Subjects.....	20
4.3.2 Exclusion Criteria for Subjects Without Retinopathy	23
4.3.3 Additional Exclusion Criteria for Subjects With Minimal Background Retinopathy	24
4.4 RECRUITMENT.....	24
5. INFORMED CONSENT	25
5.1 GENERAL PRINCIPLES	25
5.2 SEQUENCE OF PROCEDURES	26
6. PRE-RANDOMIZATION EVALUATION.....	27
6.1 GENERAL PRINCIPLES	27
6.2 LABORATORY	27
6.3 OPHTHALMOLOGIC.....	27
6.4 RENAL.....	27
6.5 NEUROLOGIC	28
6.6 CARDIOVASCULAR	28
6.7 PSYCHOLOGICAL	29
6.8 COMPLIANCE/ADHERENCE.....	29
6.9 DIETARY	30
6.10 EXAMINATION RESULTS.....	30
7. RANDOMIZATION	32
7.1 PHASE II RANDOMIZATION	32
7.2 PHASE III RANDOMIZATION	32
7.2.1 Stratification.....	32
7.2.2 Randomization Sequences	32
7.2.3 Pace of Randomization.....	33
7.3 MECHANICS OF RANDOMIZATION	33
7.4 INELIGIBLE SUBJECTS WHO ARE RANDOMIZED	33
8. METABOLIC CONTROL	34
8.1 INTERVENTION STRATEGY IN THE STANDARD GROUP.....	34
8.1.1 Intervention Strategy.....	34
8.1.2 Insulin.....	35
8.1.3 Diet.....	35
8.1.4 Exercise	35
8.1.5 Self Monitoring/Glucose	35

8.1.6	Self Monitoring/Ketone.....	36
8.1.7	Clinic Visits	36
8.1.8	Educational Program	36
8.1.9	Protection of Subjects	36
8.2	INTERVENTION STRATEGY IN THE EXPERIMENTAL GROUP	36
8.2.1	General Guidelines	37
8.2.2	Insulin.....	37
8.2.3	Diet.....	38
8.2.4	Exercise	38
8.2.5	Monitoring/Ketones.....	38
8.2.6	Blood Glucose Monitoring	38
8.2.7	Clinic Contacts.....	38
8.2.8	Protection of Subjects	39
8.3	GENERAL PROCEDURES TO MAXIMIZE ADHERENCE TO PROTOCOL	39
9.	PROCEDURES FOR FOLLOW-UP VISITS	40
9.1	GENERAL PRINCIPLES	40
9.2	BLOOD GLUCOSE CONTROL.....	40
9.3	OPHTHALMOLOGIC	40
9.4	RENAL.....	41
9.5	NEUROLOGIC	41
9.6	CARDIOVASCULAR	41
9.7	PSYCHOLOGICAL	42
9.8	COMPLIANCE/ADHERENCE.....	42
9.9	DIETARY	42
9.10	EXAMINATION RESULTS.....	42
9.11	MISSED VISITS	42
9.12	TRANSFER	43
10.	INTERNAL MONITORING.....	44
10.1	GENERAL PRINCIPLES	44
10.2	RESPONSIBILITY FOR MONITORING	44
10.3	PERFORMANCE MONITORING	45
10.3.1	Clinical Centers.....	45
10.3.2	Central Units.....	45
10.3.3	Coordinating Center.....	46
10.4	CORRECTION OF DEFICIENCIES	46
11.	INTERCURRENT EVENTS.....	47
11.1	DEFINITION OF INTERCURRENT EVENTS	47
11.2	GENERAL PRINCIPLES	47
11.3	GUIDELINES FOR THE MANAGEMENT OF INTERCURRENT EVENTS	47
12.	CHANGES IN TREATMENT.....	48
12.1	INTRODUCTION	48
12.2	MODIFICATION OF THE EXPERIMENTAL TREATMENT PROTOCOL	48
12.3	MODIFICATION OF THE STANDARD TREATMENT PROTOCOL	48
12.4	REVIEW OF MODIFICATIONS	49
12.5	DEVIATION FROM TREATMENT PROTOCOLS	49
12.6	REVIEW OF DEVIATIONS	49
12.7	TRANSFER TO INACTIVE STATUS.....	49
12.8	REVIEW OF TRANSFER TO INACTIVE STATUS.....	49
13.	RESULTS AND STATISTICAL ANALYSES.....	50
13.1	GENERAL PRINCIPLES	50
13.2	BASELINE RESULTS AND ANALYSES	50
13.3	OUTCOME VARIABLES	50
13.4	ANALYSIS PLAN	53
13.5	INTERIM ANALYSES	53
14.	PUBLICATIONS AND PRESENTATIONS.....	55
14.1	INTRODUCTION	55
14.2	DUTIES OF THE PUBLICATIONS AND PRESENTATIONS COMMITTEE	55
14.3	IMPLEMENTATION.....	56

15. ANCILLARY STUDIES	57
15.1 INTRODUCTION	57
15.2 DEFINITION OF AN ANCILLARY STUDY.....	57
15.2.1 Reason for Requirement of Approval	57
15.3 LEVELS OF APPROVAL REQUIRED FOR ANCILLARY STUDIES	57
15.4 FUNDING OF ANCILLARY STUDIES.....	58
15.5 PUBLICATION OF ANCILLARY STUDY RESULTS.....	58
15.6 IMPLEMENTATION.....	58
16. PROTOCOL CHANGES	59
16.1 INTRODUCTION	59
16.2 STEERING COMMITTEE POLICY.....	59
16.3 PROCEDURES.....	59
17. ORGANIZATION	60
17.1 INTRODUCTION	60
17.2 STRUCTURE	60
17.3 MORBIDITY/MORTALITY CLASSIFICATION COMMITTEE	64
18. DISPOSITION OF DOCUMENTS, DATA, AND MATERIALS	66
18.1 DOCUMENTS	66
18.2 DATA FORMS	66
18.3 TAPES OF DATA AND ANALYSIS FILES	66
18.4 LABORATORY SPECIMENS.....	66
18.5 PHOTOGRAPHS AND OTHER MATERIALS.....	66
18.6 POLICY OF EXTERNAL DISTRIBUTION OF DOCUMENTS DURING THE CONDUCT OF THE STUDY	67
APPENDIX A	68
APPENDIX B	74

ABBREVIATIONS USED

CBL.....	Central Biochemistry Laboratory
CHL.....	Central Hemoglobin A1c Laboratory
CMG.....	Clinic Monitoring Group
CORU	Central Ophthalmic Reading Unit
CSII.....	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DRS	Diabetic Retinopathy Study
DSQ.....	Data, Safety, and Quality Review Group
ETDRS.....	Early Treatment Diabetic Retinopathy Study
HbA1c	Hemoglobin A1c
IDDM.....	Insulin dependent diabetes mellitus
Ma.....	Microaneurysm
MDI	Multiple Daily Injection
NHLBI	National Heart, Lung and Blood Institute
NIAMDD	National Institute of Arthritis, Metabolism and Digestive Diseases
NIDDK.....	National Institute of Diabetes and Digestive and Kidney Diseases
NIH.....	National Institutes of Health
UA.....	Urinalysis
UC.....	Urine culture

SUMMARY

The purpose of the study entitled the Diabetes Control and Complications Trial (DCCT) is to compare the effects of two treatment regimens designed to produce different levels of metabolic control on the clinical course of early vascular complications in persons with insulin-dependent diabetes mellitus (IDDM). The treatment regimens are called experimental and standard. These terms are used to denote an intensive insulin regimen and a conventional insulin regimen respectively (Section 8). Blood glucose and hemoglobin A1c will be used as primary indicators of metabolic control. Diabetic retinopathy will be the principal outcome assessed because it can be reliably quantitated and its rate of progression determined in a reasonable number of years. Other outcomes will include diabetic nephropathy, diabetic neuropathy and cardiovascular events or their known or putative risk factors/

The Protocol describes a randomized, controlled, clinical trial to determine:

- whether a clinically and statistically significant difference in the level of blood glucose control between standard and experimental therapy groups as assessed by hemoglobin A1c and blood glucose measurements will result in a clinically and statistically significant difference in the rate of appearance and progression of the early vascular complications of insulin-dependent diabetes mellitus; and
- whether there is a difference in the utility, subject acceptability and safety of experimental therapy compared to standard therapy in the management of persons with IDDM>

The DCCT will focus concurrently on two categories of IDDM subjects: those who have no evidence of background retinopathy and those who have minimal background retinopathy.

At time of entry into the study, subjects with documented IDDM of 1-15 years' duration will be 13-39 years of age; have hemoglobin A1c greater than three standard deviations above the mean sample of the nondiabetic population have either no evidence, or a minimal degree of background retinopathy; and have no serious co-existing disease (Section 4). Subjects without retinopathy must have a duration of IDDM of at least one year but no more than five years and no microalbuminuria. Subjects with minimal retinopathy must have a duration of IDDM of at least one year but no more than 15 years and less than 200 mg/day of microalbuminuria.

Investigators at each clinical center will determine, through a standardized history and physical examination and a series of biochemical and psychological/behavioral determinations, whether a potential study subject is eligible for inclusion in the DCCT (Section 6). Specific criteria of eligibility for, and exclusion from, entrance into the study have been developed. Subjects who are found to be eligible for the study will undergo additional baseline assessments before randomization into a treatment group. The eligibility and baseline assessments will include hemoglobin A1c determination, blood glucose profile, a standardized ophthalmologic examination including stereo fundus photography and fluorescein angiography, and standardized renal, neurologic, cardiovascular, psychological and compliance/adherence assessments. Fully informed written consent will be obtained from each participant prior to eligibility screening and again prior to randomization (Section 5).

A total of 1400 subjects will be studied in the trial (Section 3). Subjects will be assigned randomly within each center either to the standard or the experimental therapy group (section 7).

Standard therapy will consist of not more than two injections of insulin per day with daily self-monitoring; an individualized meal plan providing for the total nutritional needs of the subject with reinforcement of the dietary program by the dietitian every six months; an education program; and a standard schedule of clinic visits and monitoring procedures every three months (Section 8.1). The aims of standard therapy include: absence of symptoms attributable to glycosuria or hyperglycemia; absence of ketonuria; maintenance of normal growth and development and ideal body weight; freedom from frequent or serious hypoglycemia; maintenance of general good health; and maintenance of hemoglobin A1c at a level less than two standard deviations above the mean value prevailing in a sample of persons with IDDM who are treated conventionally (one or two injections of insulin per day). If any of the aims are not being met, physicians will be expected to intervene using dietary reinforcement or changes of insulin within the recommended limit of two injections per day or changes in monitoring procedures. In the event that a subject in the standard group cannot achieve the treatment aims using this intervention strategy, the physician may modify the standard regimen (Section 8.1). However, more intensive management such as daily adjustment of insulin dose or frequent use of blood glucose will not be instituted or used by the Study Group for the express purpose of lowering hemoglobin A1c or blood glucose levels so long as the stated treatment aims are being met.

Individuals in the experimental treatment group will receive intensive insulin therapy in one of two ways: by subcutaneous infusion employing a pump (CSII) or administered as multiple daily injections (MDI), i.e., at least three subcutaneous injections of insulin daily (Section 8.2). The choice of method for the delivery of insulin shall rest with the DCCT treatment team and the individual subject. Either CSII, MDI, or a combination of CSII and MDI may be tried first and an alternate method employed if treatment goals are not met. For purposes of data analysis, subjects treated by CSII only, subjects treated by MDI only, and subjects treated by both CSII and MDI will constitute a single group whose outcome will be compared to those of the standard treatment group. The same principles of dietary management as outlined in the intervention strategy for the standard treatment will be followed. Reinforcement of the dietary program will be carried out by the dietitian as often as necessary to attain experimental treatment goals. Self blood glucose monitoring will be performed a minimum of four times a day, to include three preprandial and one bedtime sample. A 3:00 a.m. sample will be obtained once a week. Successive values below 65 mg/dl require the subject to contact the DCCT treatment team. Subjects will be seen weekly at the clinic until a stable treatment program is achieved and at least monthly thereafter. Telephone contact will be made daily for the first week and monthly thereafter. A system for availability of professional staff 24 hours/day will be implemented at each center.

The aim in the experimental group is to achieve and maintain glycemic control as near to normal as possible without precipitating significant hypoglycemia. This aim is defined as fasting and preprandial levels of blood glucose of 70-120 mg/dl; 90-120 minute postprandial levels less than 180 mg/dl; 3:00 a.m. blood glucose 65 mg/dl or above; and hemoglobin A1c level within two standard deviations of the mean for a sample of persons without diabetes.

During the course of the study, all participants will undergo a set of regularly scheduled procedures for subject followup and data analysis (Section 9). A standardized follow-up history and physical examination will be scheduled yearly for each subject. Determinations of

hemoglobin A1c and blood glucose profiles will be made quarterly. Stereo fundus photography will be performed at baseline and semiannually thereafter; a standardized ophthalmologic examination including visual acuity tests will be conducted yearly. Standardized psychological, neurobehavioral and compliance/adherence assessments will be made periodically (see Sections 9.6 and 9.7. Additional visits will be scheduled as needed for clinical care of the subject.

General principles are specified for the management of diabetic ketoacidosis, hypoglycemia, pregnancy and other intercurrent events (Section 11). The Protocol also describes procedures for changes in treatment (Section 12) and for protocol changes (Section 16). Policies to be employed in the statistical analysis of the data are presented in Section 13.

Mechanisms for assuring quality control and for monitoring the performance of all DCCT components on a regular basis have been established within the DCCT structure including programs for central laboratory quality control and surveillance of the clinical centers and the Coordinating Center. Two groups are specified which are advisory to the NIDDK and are otherwise external to, and independent of, the DCCT: the Policy Advisory Group (PAG) and the Data, Safety, and Quality Review Group (DSQ) (Section 17).

This Protocol is a statement of the goals and policies for Phase III of the DCCT. The details of the implementation of the Phase III study are given in the DCCT Manual of Operations.

1. INTRODUCTION

1.1 Scope and Impact of Diabetes

Diabetes is a major public health problem.¹ Approximately 5.8 million persons, about 2.6% of the United States population, have been diagnosed by a physician as diabetic. The insulin-dependent form of diabetes mellitus (IDDM) is estimated to be approximately 10% of all known cases, but virtually all diabetes diagnosed before age 20 is of this type.

Diabetes is not a benign disease. The complications of diabetes may involve every tissue of the body, but the blood vessels, nerves, kidneys, and eyes are particularly susceptible. Diabetes causes:

- 12% of all new cases of blindness;
- 25% of all kidney failure;
- 40% of all non-traumatic amputations of the foot and leg among adults.

Additionally, diabetes is one of the four major risk factors for cardiovascular disease. Heart disease, hypertension, and stroke are two to six times more likely to occur in persons with diabetes.

While complications occur in all types of diabetes, persons with IDDM may account for a disproportionate share of blindness, kidney failure, problems associated with child bearing, and premature deaths. In those with IDDM:

- 3% are legally blind after 15 years of diabetes;
- 12% are blind after 30 or more years of diabetes;
- 30% have diabetic nephropathy after 15 years of diabetes;
- 2 to 7 times more prenatal and perinatal complications and 2 to 3 times more congenital malformations occur in infants of diabetic mothers; and
- 12% are dead within 20 years after diagnosis of diabetes.

The United States ranks among the five nations in the world with the greatest mortality due to diabetes. It is the seventh leading cause of death in the United States and accounts for 150,000 deaths annually. In persons with IDDM, the majority of early deaths are due to kidney and cardiovascular diseases. Above age 20, over half of the deaths occurring in people with IDDM are due to kidney disease; this is about 500 times more frequent than in similarly aged nondiabetic persons. Deaths attributable to cardiovascular disease are about 13 times higher in persons with IDDM than in nondiabetics of similar ages. The overall mortality rate for persons with IDDM is five

¹ Extracted from statistics provided in "Diabetes in America, Diabetes Data Compiled 1984" by the National Diabetes Data Group, NIADDK, NIH.

to 11 times greater than the rates for nondiabetics of the same age; however, the risk of death markedly accelerates after age 25 to approximately 20 times that of nondiabetic persons.

Diabetes places a major drain on our health resources. Persons with diabetes have two to three times as much disability as nondiabetics and spend over twice as many days in the hospital as persons without this disease. Over 25% of all diabetics require hospitalization each year, accounting for three million hospitalizations annually and about 30 million hospital days. Additionally, about 16 million visits to physicians are made each year by persons with diabetes. It is the fourth leading cause of visits to general and family practice physicians.

Finally, the economic toll of diabetes has almost tripled in the ten years since the report of the National Commission on Diabetes. Excluding its complications, the cost in hours of work lost due to disability and premature mortality and in medical and hospital costs is at least \$14 billion.

While there is no known cure for diabetes, the future, nonetheless, looks promising for people with diabetes. Improved treatment approaches have been developed and others are under active investigation. These new approaches may lead to even better methods of treatment that will reduce the occurrence of both the acute and long-term complications. Major research advances in biomedical research have greatly expanded our understanding of the pathogenesis of diabetes and its complications. This enhanced knowledge may lead to the ability to prevent diabetes or its complications. Reducing the severity of diabetes will result in enormous savings in the human toll exacted on persons with diabetes and their families as well as the costs to society due to medical care, hospitalization, rehabilitation and economic losses due to shortened life-spans and lost days of work.

1.2 Rationale for the DCCT Study Question

One of the critical issues in diabetes mellitus has concerned the relationship between metabolic control² and the chronic complications of the disease. Controversy and debate regarding this relationship has been ongoing for 50 years.

Those who advocate the general use of rigid control (i.e., attempts to maintain blood glucose as close to normal as possible) believe that there is sufficient evidence to support the claim that such control lessens or delays the appearance of most chronic complications. Those who do not advocate the general use of rigid control contend that the evidence is inconclusive, that rigid control increases the frequency and severity of potentially dangerous side effects (e.g., hypoglycemia), and that there is some indication of potential harm (e.g., acute worsening of mild retinopathy).

Debate on the issue has centered largely on three questions:

- whether, or to what extent, the chronic complications of diabetes are related to the metabolic derangements which characterize insulin dependent diabetes mellitus;

² As used in the Protocol, "metabolic control" should be understood to mean the entire spectrum of metabolic and hormonal derangements that comprise the syndrome known as insulin-dependent diabetes mellitus. Although blood glucose control is generally used as an indicator of overall metabolic control, this is for simplicity and should not be interpreted as meaning that the DCCT investigators have equated the two.

- whether improvement of the abnormal metabolic state will lead to prevention or amelioration of the complications; and if so,
- what level of metabolic control is necessary to prevent the development or ameliorate the progression of such complications.

Conduct of the controlled clinical trial needed to resolve this issue was impeded by lack of a treatment which could achieve consistently lower blood glucose levels than those attainable with conventional therapy. In the late 1970's, technological advances in treatment approaches were made which offered significant promise for enhanced metabolic control. Experience in the application of these technologies demonstrated that it was feasible to alter the level of control achieved compared to more conventional treatment approaches. Given the capabilities available in 1985, the DCCT will test whether therapies that enable alterations of metabolic control can change the natural history of early vascular complications in persons with IDDM compared to conventional treatment approaches.

1.3 Background

In its report to the Congress in 1975, the National Commission on Diabetes recommended that the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD)³ and the National Heart, Lung, and Blood Institute (NHLBI) initiate and support a five-year clinical study to assess the effect of treatment of IDDM on the development of microvascular complications.

In 1977, the NIDDK and NHLBI convened an ad hoc committee to consider whether, how, and when such a clinical trial should be initiated. In 1978, that committee issued its report recommending that such an undertaking was both ethical and feasible and that the Institutes should proceed with a phased clinical trial to compare the effects of "strict" versus "conventional" treatment regimens. In attempting to effect this recommendation, it became clear that a conjoint study of both macrovascular and microvascular complications would not be feasible due to major differences in the natural history of the two types of complications. Accordingly, it was agreed that the NIDDK would proceed alone with the study and that the study would focus on early vascular complications.

As the planning for the study proceeded, it became increasingly clear that significant and ongoing progress in the development of new treatment approaches related to the metabolic aspects of diabetes had been made since the committee's report, notably the open loop devices for the delivery of insulin and methods for self monitoring of blood glucose concentration, and that these new technologies might offer considerable potential for achieving improved metabolic regulation. Furthermore, if they could be used in a controlled clinical trial, it might be possible to make a more clear-cut distinction between treatment groups and, thus, provide a better basis for comparison of the two treatment regimens. The NIDDK determined that initiation and implementation of such a study should be delayed so that the trial could incorporate the most current and effective methods of treatment.

In September 1980, the NIDDK convened a second group of advisors to reassess the timeliness of initiating the study. This committee issued a report reaffirming the recommendations of the first ad hoc advisory group to proceed with the study. It was further recommended that diabetic retinopathy be the principal outcome assessed in two separate groups of subjects: those

³ In 1986, the name of the Institute was changed to National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

with no evidence of background retinopathy at entry (a primary prevention group) and those with evidence of minimal background retinopathy at entry (a secondary intervention group). The rationale for studying both groups concurrently was that the secondary intervention trial would have the potential of showing a beneficial effect of one of the treatments sooner than a primary prevention trial; however, a negative result from a secondary intervention trial would not address the question posed in a primary prevention trial. Accordingly, it was recommended that both trials be undertaken simultaneously. The committee stipulated that the trial progress through sequential phases which would include a feasibility study preliminary to a full-scale trial. It was directed that the feasibility study address the utility, subject acceptability, safety and efficacy of intensive treatment regimens compared to conventional treatment regimens which might be suitable for application in a full-scale trial. The juncture between the feasibility study and the full-scale trial was to serve as a major decision point at which time a detailed assessment of the results of the feasibility study would be conducted by an independent group of expert advisors. The decision regarding initiation of a full-scale, long-term clinical trial would be based on this advice. The committee urged that the NIDDK proceed as quickly as possible to initiate the feasibility study.

Acting upon this recommendation, in 1981 the NIDDK issued a Request for Research Cooperative Agreement Applications for clinical centers and a Request for Proposals for a Data Coordinating Center willing to participate in a study consisting of the following four phases:

- Phase I -- Planning (6-12 months)
- Phase II -- Feasibility Study (2 years)
- Phase III -- Full-Scale Clinical Trial (7-10 years)
- Phase IV -- Data Analysis/Reporting (1 year)

Twenty-one clinical centers in the United States and Canada and a Data Coordinating Center were subsequently selected to participate in the study on the basis of scientific peer review.

Phase I (Planning) was initiated in March 1982 for the purposes of designing the Phase II Protocol (DCCT Research Group, 1986), assembling the Manual of Operations and establishing certification requirements for the clinical centers, central laboratories and reading and coding units preparatory to recruitment of subjects. The nomenclature specified for the two treatment groups in the DCCT was: experimental to denote the intensive treatment regimen and standard to denote the conventional treatment regimen.

Phase II (Feasibility) commenced in August 1983 and was completed in March 1985. The specific objectives of Phase II were the following:

1. To determine whether a well-informed cohort of subjects, comprising both adolescents and adults who fulfilled all the stringent eligibility criteria, could be recruited in a reasonable period of time.
2. To determine whether both a clinically meaningful and statistically significant difference in the level of blood glucose control could be achieved between the randomly assigned standard (conventional) and experimental (intensive) therapy groups, as assessed by hemoglobin A1c (HbA1c) and blood glucose measurements, while maintaining both treatment groups within acceptable ranges of glycemic control.

3. To determine the safety of the two therapies with major emphasis on assessment of: symptoms attributable to hyperglycemia, episodes of ketoacidosis, and episodes of hypoglycemia.
4. To determine whether the randomly assigned therapies would be equally acceptable to subjects as assessed by measures of adherence to the randomly assigned therapies over time and completeness of followup.
5. To determine whether biochemical and pathological characteristics of IDDM could be measured and documented with acceptable precision and accuracy.

Two hundred seventy-eight subjects were enrolled in the feasibility study. By March 1985, the data from 12 months of followup on all subjects had been collected (DCCT Research Group, 1986). These data were independently reviewed by two separate expert advisory groups. Both groups found that by all essential criteria, the feasibility objectives had been met and recommended that the NIDDK proceed with Phase III of the DCCT utilizing the protocol developed for the feasibility study with appropriate modifications.

In October 1985, the NIDDK notified the DCCT Study Group that a decision had been reached to proceed with Phase III, the full-scale clinical trial. In November 1985, a Request for Research Cooperative Agreement Applications was issued for additional clinical centers to participate in Phase III. Six additional centers were selected on the basis of peer review bringing the total number of participating clinical centers to 27 for Phase III of the DCCT.

1.4 Future Directions

The outcome of the DCCT will influence the course and direction of clinical management of persons with insulin-dependent diabetes. Recruitment of subjects will continue until the full cohort of 1400 is reached. It is planned that followup of all subjects will continue until the fifth anniversary of the last subject randomized.

An independent external group of scientific peers will review all emerging study data at regular intervals for subject safety and data quality and report to a second body of independent scientific peers. The latter group is charged with recommending to the Director of NIDDK the continuation or termination of this study, a decision to be based on careful consideration of the information resulting from the emerging data.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group: The Diabetes Control and Complications Trial (DCCT). Design and Methodological Considerations for the Feasibility Phase. Diabetes 35:530-545, May 1986.
2. The Diabetes Control and Complications Trial Research Group: The Diabetes Control and Complications Trial (DCCT). Results of the Feasibility Study (Phase II). Diabetes Care 10:1-19, January-February 1987.

2. OBJECTIVES AND DESIGN

2.1 Objectives

The major objective of the DCCT will be to compare the effect of an experimental and a standard approach to the control of blood glucose on early vascular complications in persons with IDDM.

Principal Objectives:

1. To compare the following separately for the
 - a) Primary Prevention Trial: Rate of onset and progression of diabetic retinopathy; and for the
 - b) Secondary Intervention Trial: Rate of progression of pre-existing mild non-proliferative diabetic retinopathy.
2. To compare the rate of major adverse events associated with the treatment of diabetes or participation in the trial.

Other Objectives in Both Trials:

1. To compare the rate of onset and progression of nephropathy.
2. To compare the rate of onset and progression of neuropathy.
3. To compare the rate of onset and concomitant progression of retinopathy, neuropathy, and nephropathy.
4. To compare the incidence of cardiovascular events and their known or putative risk factors.

Operational Objectives in Both Trials:

1. To recruit and randomize the numbers of subjects required to provide adequate statistical power for both trials.
2. To maintain both a clinically and statistically significant difference in the level of blood glucose control between the randomly assigned standard and experimental therapy groups as assessed by hemoglobin A1c (HbA1c) and blood glucose measurements.
3. In treatment of individual subjects in both groups to maintain clinical well-being, to maintain glycemia below predefined limits, and to minimize the occurrence of severe hypoglycemia.
4. To maintain acceptable levels of adherence to the randomly assigned standard and experimental therapies as assessed by measures of adherence over time, including completeness of followup.

5. To monitor and maintain the precision and accuracy of the assessments of the biochemical and pathological characteristics of IDDM.

The variables to be employed to address all the above objectives will be defined more precisely in Section 13, Statistical Analyses.

Natural History Objectives:

To describe the natural history of IDDM among subjects who receive the experimental therapy and among subjects who receive the standard therapy. This includes the evaluation of the above objectives within subgroups of subjects defined on the basis of age, gender, duration of IDDM, entry C-peptide, level of blood glucose and HbA1c, blood pressure, renal status, serum lipids, and other factors suspected to be associated with the risks for the development of complications of IDDM.

2.2 Design

In accordance with these objectives, the DCCT has the following design features:

1. All 278 subjects recruited for the feasibility study will continue to be followed until completion of the study in either the primary or secondary trial as indicated by post-randomization stratification on the subjects baseline retinopathy status.
2. Additional subjects will be recruited over a period of three years and their eligibility determined (see Section 4). Subjects without evidence of diabetic retinopathy suitable for a primary prevention trial and subjects with evidence of minimal retinopathy (see section 4) suitable for a secondary intervention trial will be recruited.
3. Eligible and consenting subjects in each of the clinical centers will be assigned randomly to receive either standard or experimental therapy.
4. A total of 1400 subjects will be randomized within two retinopathy strata with approximately equal numbers in each stratum.
5. This sample size provides power >0.91 to detect a 32.5 to 37.5% reduction in the annual hazard for the onset or progression of diabetic retinopathy allowing for 10% loss of followup and 20% nonadherence to assigned treatment.
6. For the primary prevention trial, the preferred outcome measure is a compelling clinically defined event such as proliferative diabetic retinopathy (PDR). However, the incidence of such an outcome in this population is low, even with the planned ten-year followup. Therefore, the sample size required to achieve a statistically significant result would be excessive. Thus, a different outcome measure is needed. This measure needs to accurately reflect the underlying physiological process of worsening of retinopathy and have an event rate higher than that for PDR. Thus, the DCCT has selected the appearance of any retinopathy, defined as the onset of persistent microaneurysms, as the outcome measure upon which the sample size is based. Therefore, the study has less power to detect treatment group differences at the more clinically meaningful levels of retinopathy. Nevertheless, a treatment group difference

with respect to the appearance of any retinopathy will be evaluated in consideration of its consistency with a treatment effect at more clinically meaningful levels.

7. Standard therapy will consist of not more than two injections of insulin daily. The dose and insulin mixture will be determined on an individual basis by the physician. Clinical well-being is the first priority. Special efforts will be made to insure that the subjects hemoglobin A1c does not exceed two standard deviations above the mean of a sample of IDDM subjects (13.11%) and that all criteria for good clinical health are met.
8. Experimental therapy will permit the subject and his/her physician to choose either multiple daily injections of insulin (MDI) or a continuous subcutaneous infusion of insulin (CSII) or a combination. Both will employ frequent self blood glucose monitoring and will strive to maintain hemoglobin A1c levels within two standard deviations of the mean for a sample of persons without diabetes (6.05%, mean \pm 2 S.D.).
9. All subjects will be analyzed according to their original treatment assignment and all efforts will be made to treat subjects according to their assignment until the end of the study. Changes in treatment are discussed in Section 12.
10. All subjects will be followed at least until the fifth year after enrollment in the study or until the study is terminated. Thus, some subjects will be followed for up to ten years while others will be followed for less and varying lengths of time.
11. All study personnel are masked to study outcomes, therefore, two independent advisory groups will review periodically the study results and are authorized to recommend to the NIDDK that the trial be terminated if the study objectives have been met. However, clinical thresholds for safety have been created and appropriate personnel will be alerted when a patient passes a threshold.
12. Clinical, physical, and biochemical evaluations will be conducted prior to randomization and periodically during followup according to the schedule depicted in Table 2.1.
13. The two treatment regimens will, of necessity, be conducted in an unmasked manner. With the exception of HbA1c, all centrally determined outcome measurements will ordinarily be masked from the investigator responsible for the treatment regimens and from the subjects. The results of these centrally determined outcome measurements relating to complications will be reported as "within acceptable limits" when no therapeutic intervention is indicated. In the event that an outcome measurement would dictate a change in subject management, the results will be promptly communicated to the responsible investigator who will inform the subject and institute appropriate therapy.

Hemoglobin A1c values will be unmasked in the experimental group because the treatment regimen is directed toward achieving specific values. Hemoglobin A1c values will ordinarily remain masked in the standard group because the treatment regimen is not directed toward achieving specific values. However, in this group, subjects with HbA1c values that exceed the upper action limit of two standard deviations above the mean of samples of IDDM subjects (13.11%) will be reported monthly to the investigator until the situation is corrected (see Section 8).

Table 2.1

June 1988

Diabetes Control and Complications Trial
Schedule of Patient Evaluation for Endpoint Analyses

EXAMINATIONS	BASELINE	1 YR	2 YR	3 YR	4 YR	5 YR	6 YR	7 YR	8 YR	9 YR or LAST
GENERAL										
History and Physical Exam	X	X	X	X	X	X	X	X	X	X
BLOOD GLUCOSE CONTROL										
Home Blood Glucose Profile (Baseline, quarterly, annually)	X	X	X	X	X	X	X	X	X	X
HbA1c (Baseline, quarterly, annually)	X	X	X	X	X	X	X	X	X	X
OPHTHALMOLOGIC										
Visual Acuity	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure	X	X	X	X	X	X	X	X	X	X
Slit Lamp	X	X	X	X	X	X	X	X	X	X
Ophthalmologic Exam	X	X	X	X	X	X	X	X	X	X
Stereo Fundus Photography (Baseline, semiannually, annually)	X	X	X	X	X	X	X	X	X	X
Stereo Fluorescein Angiography*	X					X				X
RENAL										
Microalbuminuria	X	X	X	X	X	X	X	X	X	X
Creatinine Clearance	X	X	X	X	X	X	X	X	X	X
I-125 Iothalamate Clearance	X			X						X
Serum Creatinine, Albumin	X	X	X	X	X	X	X	X	X	X
Urine Creatinine, Albumin	X	X	X	X	X	X	X	X	X	X
Sodium urea and nitrogen and urine creatinine 24-hour urine collection)	X		X			X				X
NEUROLOGIC										
Standardized Symptom History & Physical Exam	X					X				X
Autonomic Nervous System Function Tests (RR-Variation on EKG)	X		X		X		X		X	
Noninvasive Nerve Conduction	X					X				X
CARDIOVASCULAR										
History & Physical (Including Peripheral Vascular History & Physical Exam)	X	X	X	X	X	X	X	X	X	X
Blood Pressure, Pulse (Baseline, quarterly, annually)	X	X	X	X	X	X	X	X	X	X
Resting EKG	X		X		X		X		X	
Serum Triglycerides	X	X	X	X	X	X	X	X	X	X
Serum Total Cholesterol, HDL, Calculated LDL	X	X	X	X	X	X	X	X	X	X
PSYCHOLOGICAL										
Neurobehavioral Assessment										
Full	X		X			X		X		X
Psychological Symptoms (SCK-90-R)	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaire	X	X	X	X	X	X	X	X	X	X
COMPLIANCE/ADHERENCE										
Assessment of Adherence (Baseline, quarterly, annually)	X	X	X	X	X	X	X	X	X	X
Diet History	X		X			X				X

*Stereo fluorescein angiography will be performed only in those patients in the primary prevention trial.

Note Bene: Assessment of blood glucose control is performed quarterly. Stereo fundus photography is performed at baseline, six months post-randomization, and every six months thereafter. Assessment of blood pressure, pulse and adherence are performed quarterly.

3. SAMPLE SIZE

3.1 Introduction

The principal objective of the DCCT is to evaluate the difference between the standard and experimental therapies in the resulting rate of the development of the early vascular complications of diabetes. The initial Request for Applications issued by the NIDDK indicated that the onset of retinopathy or the worsening of pre-existing retinopathy would constitute the principal outcome measure for the trial. Diabetic retinopathy was chosen because the natural history of this IDDM complication has been described (Frank, et al, 1980; Palmberg, et al, 1981; Klein, et al, 1984) and because accurate and reproducible methods have been developed for the assessment of this lesion in multi-center clinical trials using fundus photography (DRS, 1981).

As described in Chapter 13, one of the principal analyses to be conducted is the life table analysis of the time to onset of retinopathy among subjects in the primary prevention trial (no retinopathy on entry), and the life table analysis of the time to worsening of retinopathy among those in the secondary intervention trial (minimal background retinopathy on entry). In these analyses, the cumulative incidence curves will be estimated separately for the experimental and standard groups by the life table method and the curves will be compared using the non-parametric linear rank test. The power function of the linear rank test for the comparison of life tables was used to evaluate the power of the study to detect clinically relevant differences in the rate of onset or of progression of retinopathy.

The power of the linear rank test can be evaluated in terms of an exponential model (cf. Lachin, 1981). Under an exponential model, the cumulative incidence $P(t)$ at time t can be obtained as

$$P(t) = 1 - e^{-\lambda t}$$

where λ is the hazard rate per unit of time per year. The hazard rate is the probability that the event will occur during a year given that the event had not yet occurred at the beginning of the year. Each value of the hazard rate λ , such as $\lambda = 0.20$, describes a complete cumulative incidence curve as t increases from 0 to 1, 2, . . . years. Thus, with this model, the difference between the cumulative incidence curves estimated by the life-table method for two groups can be described in terms of the difference between the hazard rates for the two curves.

3.2 Natural History of Retinopathy

Various cross-sectional studies present estimates of the prevalence of retinopathy as a function of years of duration of IDDM (Frank, et al, 1980; Palmberg, et al, 1981; Klein, et al, 1984). In addition, the study by Klein, et al (1984) included the prospective evaluation of progression of retinopathy after two and six additional years of followup among subjects with minimal retinopathy on entry who were comparable to those to be recruited for the DCCT. These studies allow an evaluation of the expected rate of onset of retinopathy among those in the primary prevention trial, and the rate of progression of retinopathy among those in the secondary intervention trial.

In the primary prevention trial, subjects entering the DCCT will have a duration of diabetes from one to five years, with an average of three years duration on entry. For such subjects who

receive standard therapy, these studies suggest that 50% of subjects will develop retinopathy (at least 1 microaneurysm) after an additional 3.5 years of followup in the trial. Under an exponential model, this corresponds to a constant annual hazard rate of about $\lambda = 0.20$ per year of followup. In the secondary intervention trial of subjects with one to 15 years duration of IDDM and minimal retinopathy on entry, the prospective study of Klein, et al (1984) suggests that about 20% of subjects who receive standard therapy will progress (three steps on the DCCT retinopathy scale) after two additional years of followup, and 65% after six years. This also corresponds to a constant annual hazard rate of about $\lambda = 0.20$ per year of followup.

Thus, for both the primary prevention and secondary intervention trials, it is estimated that the hazard rate for retinopathy would be approximately $\lambda = 0.20$ per year of followup in the DCCT among subjects treated in the standard therapy group. In both the primary prevention and secondary intervention trials, a hazard rate of $\lambda = 0.20$ implies that about 45% of these subjects will show progression of retinopathy after three additional years of followup in the DCCT, 63% after five years, and 75% after seven years.

3.3 Study Duration and Sample Size

Based on the assumption of $\lambda = 0.20$ for both the primary prevention and secondary intervention trials, it was then possible to consider the period of recruitment, total study duration and total sample size. This is a recursive process, however, because the power of study depends upon the total number of events to be observed which is influenced by all three of the above factors. After considering various combinations, it was decided that a study of 1400 patients total, 700 in each of the primary prevention and secondary intervention trials, the remainder recruited over a three year period, and with followup for an additional five years, would provide excellent power to detect clinically meaningful differences between the treatment groups.

In order to provide an accurate description of the cumulative incidence of the onset of retinopathy within the primary prevention trial and of the progression of retinopathy in the secondary intervention trial, it was decided that the minimum period of followup for all subjects would be five years. In addition, it was decided that a three year period of recruitment would be provided for the 21 Phase II clinics and that it would be expected that these clinics would recruit a total of 1156 subjects, including those already recruited during Phase II.

In addition, new clinics will be added to the study group which will be expected to recruit 244 additional subjects over a two year period. The last subjects to be recruited will enter the trial in September 1988, and since all subjects will be followed for at least five years, this means that these last subjects will complete followup in September 1993.

Thus the total sample size objective for the DCCT is 1400 subjects, 700 in each of the primary prevention and secondary intervention trials, with a minimum duration of followup for all subjects of five years. However, since some subjects were recruited into Phase II in August 1983, followup of all subjects until September 1993 entails that some subjects will be followed for up to ten years. Therefore, the length of followup for each subject will range from five to ten years, depending on when the subject entered the trial. The average duration of followup will be seven years.

The study will actually comprise three cohorts of subjects: the Phase II subjects recruited within the original 21 clinics, the Phase III subjects recruited in the original 21 clinics, and the

Phase III recruited among the new clinics. For each cohort, the following presents the time intervals of recruitment, the length of the recruitment period, the total duration of study for each cohort, and the expected sample sizes to be recruited.

Cohort	Recruitment Interval	Recruitment Period (years)	Study Period (years)	Sample Size	
				Primary	Secondary
1) Phase II, 21 clinics	8/83 – 3/84	0.5	10.0	110	168
2) Phase III, 21 clinics	3/85 – 3/88	3.0	8.5	468	410
	9/86 – 9/88	2.0	7.0	<u>122</u>	<u>122</u>
TOTAL				700	700

Thus the first few subjects recruited into Phase II in August 1983 will have been followed for ten years; the first subjects recruited by the original 21 clinics into Phase III will be followed for 8.5 years; and the first subjects recruited by the new clinics will be followed for seven years. The last subject recruited by the new clinics will be followed for 5 years. For all subjects combined, the following presents the numbers of subjects expected to be followed for varying durations:

- ≥ 5 years: all 1400 subjects
- ≥ 6 years: 1172 of the 1400 subjects
- ≥ 7 years: 798 of the 1400 subjects
- ≥ 8 years: 426 of the 1400 subjects
- ≥ 9 years: 278 of the 1400 subjects

Since the majority of the subjects will be followed for at least seven years, this will allow accurate description of the cumulative incidence curves within the standard treatment group over the first seven years of followup, by which time the cumulative incidence for the onset or progression of retinopathy is expected to reach 75% based on a hazard rate of $\lambda = 0.20$ per year of followup.

3.4 Power

In the final analysis of the DCCT data, the cumulative incidence curves will be estimated by the life-table method for the standard and experimental groups and the curves compared using the linear rank test. Lachin and Foulkes (1986) describe the evaluation of the power of the linear rank test using the exponential model for the detection of differences between the cumulative incidence curves for two groups, where the subjects are recruited in two or more cohorts, with allowances both for losses to followup and for non-compliance. In this context, losses to followup are subjects for whom endpoint evaluations (fundus photographs) are no longer available, whereas non-compliance refers to subjects who did not fully comply with the assigned regimen but who continue followup in the trial.

The principal determinant of the power of the linear rank test is the minimal difference between the hazard rates for the two groups which it is desired to detect. It must be emphasized that it is of interest to the trial to detect either a significant increase or decrease in the incidence of onset or of progression of retinopathy. Thus, a two-sided test of significance is to be employed.

However, for purposes of examining a difference in hazard rates, it is more conservative to consider a reduction in the hazard rate for the experimental group rather than an increase in the hazard rate.

As described above, it is estimated that the hazard rate for the standard treatment group in either the primary prevention or the secondary intervention trial is expected to be $\lambda = 0.20$ per year of followup. The trial was then designed to provide a high degree of power to detect a reduction in the hazard rate of onset or progression of retinopathy in the experimental treatment group from $\lambda = 0.20$ to the range $0.135 > \lambda > 0.125$ per year of followup, i.e., a 32.5% to 37.5% reduction in the annual hazard rate. The cumulative incidence as a function of years of followup for each of these hazard rates is as follows:

t years followup	Standard	Experimental	
	$\lambda = 0.20$	$\lambda = 0.135$	$\lambda = 0.125$
1	0.18	0.13	0.12
2	0.33	0.24	0.22
3	0.45	0.33	0.31
4	0.55	0.33	0.31
5	0.63	0.51	0.46
6	0.70	0.56	0.53
7	0.75	0.61	0.58

Since all 1400 subjects will be exposed for five years of followup, 1172 for six years, 798 for seven years, etc., it is possible to estimate the overall simple proportions of subjects in whom the onset or progression of retinopathy will be observed in each group. The following are the simple proportions expected to be observed in the standard group ($\lambda = 0.20$) and in the experimental group ($0.135 > \lambda > 0.125$), assuming 0% and 10% losses to followup, and assuming 0% and 20% non-compliance:

% losses / % non-compliance	Expected Simple Proportions		
	<u>Standard</u>	<u>Experimental</u>	
	$\lambda = 0.20$	$\lambda = 0.135$	$\lambda = 0.125$
0% / 0%	0.77	0.63	0.61
10% / 0%	0.72	0.58	0.56
10% / 20%	0.72	0.61	0.58

Note that 10% losses to followup results in a constant reduction in the expected proportions for each group, whereas 20% non-compliance results in a narrowing of the difference between the expected proportions for the standard and experimental groups.

Table 3.1 presents the power of the primary prevention and secondary intervention trials to detect the above minimal differences in hazard rates with the above corresponding reductions in the cumulative incidence, or simple proportions, of onset and of progression of retinopathy. Power is presented both assuming a two-sided test at the 0.05 significance level and also at the 0.01 significance level. The first column presents the power of the study if it is assumed that there are no subjects who are lost to followup and all subjects are fully compliant. In this case, the study is almost certain to detect differences at these levels in the cumulative incidence curves for the two treatment groups. It is unrealistic to expect, however, that all subjects will continue followup and that all subjects will comply. The next column presents the power of the study assuming that 10% of subjects are lost to followup, but that all subjects who continue treatment fully comply with the assigned regimen. In this case, the power is slightly reduced due to the loss of 10% of subjects over the period of study, but the study would still have excellent power to detect these differences. The final column, however, presents a more realistic assessment of power which includes an allowance for 10% of subjects being lost to followup and 20% of subjects failing to comply with the assigned regimen. In this case, both the primary prevention and secondary intervention trials would provide excellent power (≥ 0.90) for the detection of a 37.5% reduction in the hazard rate from 0.20 to 0.125 using either the 0.05 or the 0.01 significance level. If a 0.05 significance level is employed, the study also provides excellent power (0.91) to detect a 32.5% reduction in the hazard rate from 0.20 to 0.135. However, using the 0.01 significance level, the power of the study will be good, but not excellent, (0.77) to detect this smaller reduction in the hazard rate.

3.5 Interim Assessments

The plan described above indicates that the study will have excellent power to detect meaningful differences between the treatment group .us provided that the stated assumptions apply. These assumptions are that the hazard rate for the onset of retinopathy in the primary prevention trial is 0.20 per year, the hazard rate for the progression of retinopathy in the secondary intervention trial is also 0.20 per year, all additional patients are recruited during the allocated intervals, no more than 10% of patients are lost to followup, and no more than 20% of patients are non-compliant. Each of the above parameters will be monitored by the Study Group as the study progresses. If it is determined that one or more of these assumptions are not accurate, then adjustments will be implemented to insure that the excellent power of the study will be maintained. Such adjustments may entail a change in the target sample size for either the primary prevention or secondary intervention trials, or a change in the duration of followup. For example, more patients and/or a longer study duration may be required if the observed hazard rate in either the primary prevention or secondary intervention trial is substantially less than 0.20 per year. Conversely, fewer patients and/or a shorter duration of followup may be required if the hazard rate is substantially greater than 0.20 per year.

3.6 Summary

The target sample size for the DCCT is 700 subjects for each of the primary prevention and secondary intervention trials. The principal outcome is the rate of onset of retinopathy in the primary prevention trial, and the rate of progression of retinopathy in the secondary intervention

trial. The cumulative incidence of these events will be described by life-table analyses. Such analyses can be summarized by the hazard rate which is the probability of new events per year of followup. The hazard rate is expected to be 0.20 per year for the standard group in both the primary prevention and secondary intervention trials. The DCCT has been designed to detect a 32.5%-37.5% change in the hazard rate in the experimental group. Allowing for 10% of subjects being lost to followup and 20% of subjects not complying with therapy, the study provides power >0.91 to detect these changes with a test at the 0.05 significance level (two-tailed) in both the primary prevention and secondary intervention trials. For a test at the 0.01 level (two-tailed), the study provides power = 0.77 to detect the smaller 32.5% change in the hazard rate, and power = 0.91 to detect the larger 37.5% change in the hazard rate. The assumptions on which these calculations of power are based (hazard rate of 0.20 per year, full recruitment in three years, no more than 10% lost to followup, and no more than 20% non-compliance) will be monitored during the trial, and the target sample size or study duration may be modified if actual experience in the DCCT differs from these estimates.

REFERENCES

1. Diabetic Retinopathy Research Group: Report 7. A modification of the Airlie House classification of diabetic retinopathy. Invest Ophthalmol Vis Sci 21/2:244-51, 1981.
2. Frank RN, Hoffman WH, Podgor MJ, et al. Retinopathy in juvenile-onset diabetes of short duration. Ophthalmol 87:1-9, 1980.
3. Palmberg P, Smith M, Waltman S, et al. The natural history of retinopathy in insulin-dependent juvenile-onset diabetes. Ophthalmol 88:613-8, 1981.
4. Klein R, personal communication based on the study described in: Klein R, Klein BE, Moss SE, et al. Prevalence of diabetes mellitus in southern Wisconsin. Am J Epidemiol 119:54-61, 1984.
5. Lachin J. Introduction to sample size determination and power analysis for clinical trials. Controlled Clinical Trials 2:93-113, 1981.
6. Lachin J and Foulkes M. Evaluation of sample size and power for analyses of survival with allowances for non-uniform subject entry, losses to followup, non-compliance and stratification. Biometrics, 42:507-519, 1986.

Table 3.1

Power of the DCCT to detect reductions in the hazard rate of onset of retinopathy in the primary prevention trial (P), and reductions in the hazard rate of progression of retinopathy in the secondary intervention trial (S), with a total sample size of 700 subjects within each stratum.

		% Losses to Followup / % Non-compliance		
		0% / 0%	10%/ 0%	10% / 20%
$\alpha = 0.05^+$				
0.20 vs 0.135 ⁺⁺	P	0.990	0.985	0.910
	S	0.991	0.986	0.913
0.20 vs 0.125	P	0.999	0.998	0.973
	S	0.999	0.998	0.974
$\alpha = 0.01^+$				
0.20 vs 0.135	P	0.957	0.939	0.767
	S	0.959	0.942	0.772
0.20 vs 0.125	P	0.993	0.989	0.906
	S	0.994	0.989	0.909

⁺Two-tailed

⁺⁺The hazard rate for the standard vs experimental groups per additional year of followup in the DCCT. The hazard rate is the probability of new events per year of followup.

4. SUBJECT SELECTION AND RECRUITMENT

4.1 Introduction

Investigators at each participating clinical center will determine by a series of screening interviews and examinations whether a potential study participant is eligible for inclusion in the DCCT. Each clinical center will recruit individuals for the primary prevention and the secondary intervention trials.

4.2 Eligibility Criteria

The following conditions must be satisfied for a volunteer to be considered eligible for the Phase III study.

4.2.1 Eligibility Criteria Applicable to All Subjects

1. Age greater than or equal to 13 years and less than 40 years at time of randomization. Adolescents must be at or beyond the Tanner Stage II level of pubertal development.
2. An HbA1c value greater than three standard deviations above the mean of a sample of non-diabetic persons (6.55). This criterion is based on the first measurement obtained during the pre-randomization evaluation process and exclusion on its basis is applicable for a period of six months. If, in the opinion of the investigator the value is clearly inconsistent with self blood glucose measurements or local HbA1c values, a second measurement can be obtained within two weeks of notification of the first value.
3. Informed consent from participants 18 years or older. Informed consent from participants aged less than 18 years and, additionally, informed consent from the parent or guardian.
4. Serum creatinine less than or equal to 1.2 mg/dl, or, at investigators discretion, creatinine clearance greater than or equal to 100 ml/min/1.73m².

4.2.2 For Subjects Without Retinopathy

1. Duration of IDDM for at least one year but less than or equal to five years.
2. Absence of diabetic retinopathy or other ocular lesions which would confound the assessment of retinopathy or other aspects of ocular status based on central grading of stereo fundus photographs.
3. Visual acuity of 50 letters (20/25 Snellen equivalent) or better in both eyes (best corrected) using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts and protocol.

4. Less than 40 mg. albumin/24 hour on a four-hour standardized urine collection.

4.2.3 For Subjects With Minimal Background Retinopathy

1. Duration of IDDM for at least one year but less than or equal to 15 years.
2. Presence of at least one microaneurysm in either eye with or without other diabetes related lesions, but less retinopathy than would characterize either eye as P2⁴ or worse based on central grading of stereo fundus photographs.
3. Visual acuity of 45 letters (20/32 Snellen equivalent) or better in both eyes (best corrected) using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts and protocol.
4. Less than or equal to 200 mg. albumin/24 hour on a four-hour standardized urine collection.

4.3 Exclusion Criteria

In order to be eligible for this study, the subject must be free of the excluding diseases and conditions itemized below. For some of these diseases, the diagnosis can be made on objective grounds. In other cases, it will not be possible to follow rigid criteria, and the diagnosis must rest upon the considered judgment of the examining physician. Hospital records will be used as extensively as possible to document the historical material reported by the subject. Some of these conditions will exclude the subject permanently from the study. Other conditions may only temporarily exclude, and the subject may be reconsidered for eligibility for the study at some later date.

4.3.1 Exclusion Criteria Applicable to All Subjects

1. Clinical characteristics of IDDM but subjects with more than five years duration of IDDM are excluded if their centrally measured basal or stimulated C-peptide is greater than .2 pmol/ml. Subjects with five years or less duration of IDDM are excluded if their centrally measured stimulated C-peptide is greater than .5 pmol/ml or basal C-peptide is greater than .2 pmol/ml. The basal specimens are considered stimulated if the centrally measured basal blood glucose is greater than 150 mg/dl.
2. Previous treatment for IDDM with either three or more daily injections of insulin or with an insulin infusion pump except for periods of less than four weeks to manage an intercurrent illness or to determine optimal blood glucose control. An exception will be made for women who used intensive therapy only during a pregnancy and/or planning

⁴ Classification of eyes is based on Diabetic Retinopathy Study (DRS) criteria. Eyes with new vessels are worse than P2. Eyes without new vessels which meet specified criteria are classified as P2. Standard photos are those of the Modified Airlie House Classification.

- for the pregnancy and who will have been on one or two injections of insulin for at least the year prior to randomization.
3. Insulin Resistance: Requirement of a total of more than two units per kilogram of body weight except during intercurrent illnesses lasting less than one month.
 4. Three or more documented episodes of diabetic ketoacidosis requiring hospitalization during the 12 months prior to the time of randomization.
 5. Women who are pregnant or who plan or desire a pregnancy within two years of the time of randomization.
 6. Hypertension
 - a) Subjects who required treatment of hypertension during the two years prior to the time of randomization are ineligible for the trial.
 - b) In adults, sitting blood pressure greater than 140 systolic or 90 diastolic without treatment at the time of the eligibility history and physical examination.
 - c) In adolescents, sitting blood pressure greater than the 95th percentile above the mean for proper category of age and sex as defined in the Report of the Task Force on Blood Pressure in Children⁵.
 7. Lipids
 - a) 2 History of treatment for hyperlipidemia not secondary to diabetes.
 - b) Serum cholesterol greater than three standard deviations above the mean for sex and age as defined in the Lipid Research Clinic Population Studies Data Book Volume I of the Prevalence Study.
 - c) Calculated LDL-cholesterol greater than 190 mg/dl when total serum cholesterol is below the mean plus three standard deviations but greater than 265 mg/dl.
 8. Active urinary tract infection as indicated by urine abnormalities specified in the Manual of Operations.
 9. History of alcoholism or drug abuse during the five years prior to randomization as defined by the DSM III classification for substance abuse as defined in the Manual of Operations.
 10. Any non-diabetic condition that potentially limits life expectancy or that will interfere with participation in the study.
 11. Residence at a distance from the clinic that presents a likely impediment to complete followup or a planned permanent move outside of North America.

⁵Pediatrics, Vol. 59, Supplement 1, 1977.

12. Any form of hemoglobinopathy or hemolytic process which interferes with reliable assessment of diabetic control with conventional assays for glycosylated hemoglobin (e.g., sickle trait).
13. Diabetic Neuropathy - Subjects requiring or requesting treatment for diabetic neuropathy at the time of entry into the trial.
14. Previous or current endocrine disorder other than diabetes, corrected primary hypothyroidism, or functional menstrual disorders. Persons with corrected hyperthyroidism with greater than two years of an euthyroid state at the time of randomization and no past or present ophthalmopathy are eligible to be in the DCCT.
15. Obesity defined as a body weight greater than 130% of the ideal body weight as defined by the 1983 Metropolitan Height and Weight Tables for Men and Women and adjusted for frame size as defined in the DCCT Manual of Operations. Tables are taken from the data of the 1979 Build Study, Society of Actuaries and Association of Life Insurance Medical Directors of America, 1980 (see the Manual of Operations).
16. Chronic disease requiring prescription medication for more than a total of four months during the twelve months prior to randomization. (See the Manual of Operations for a detailed list of excluding medications and disqualifying diseases.)
17. Major electrocardiographic abnormalities or clinical history of ischemic (coronary) heart disease or subjects with symptomatic peripheral vascular disease.
18. History of epilepsy or seizures (not caused by hypoglycemia) requiring medication during the five years prior to randomization.
19. Psychological and Behavioral Criteria
 - a) Psychological problems such as psychotic, neurotic or personality disorders and conditions that will interfere with the ability to maintain complete followup and adhere to the Protocol, or
 - b) A recent pattern of behavior that, in the opinion of the Principal Investigator, indicates a high likelihood of non-compliance, e.g., missed appointments during the pre-randomization phase or inability to follow other instructions such as those detailed in the Manual of Operations.
20. Siblings, parents, children, spouses, or other household members (a) of subjects who have been randomized into Phase II or III, or (b) of clinic staff members. Clinical center staff members are also excluded.
21. Participation in another clinical trial or any study which may interfere with participation in this trial.
22. Any condition or use of any medication which will interfere with the application of treatment as outlined in the Protocol.
23. For adolescents, history of or demonstrated failure to maintain normal growth and development two years prior to randomization for any reason, i.e., growth velocity less

than the third percentile of normal for age, sex and pubertal stage according to the National Center for Health Statistics Growth Curves for Children, Birth - 18 years, United States, Vital and Health Statistics, DHEW Publication, No. 78-1650, November 1977 (see the Manual of Operations). If previous reliable growth records are not available, failure to maintain growth at a rate of at least 4 cm. or 1.60 inches per year during the previous six months unless pubertal stage (i.e., menarche in females and Tanner IV in males) indicates that growth is complete.

24. Hypoglycemia

- a) 2 More than two hypoglycemic seizures and/or comas during the previous two years.
- b) More than one hypoglycemic episode in the past two years resulting in cerebral impairment (e.g., coma, severe confusion, seizure) before the development of warning symptoms of hypoglycemia while awake (e.g., excessive sweating, tremors, etc.).

25. The presence of significant chorioretinal scars, optic atrophy, retinal degeneration, or other conditions which might confound the assessment of ocular status.

26. Aphakia in one or both eyes or prior ocular surgery other than strabismus or lid surgery.

27. Intraocular pressure greater than or equal to 23 mm of mercury in one or both eyes, or glaucoma requiring medication.

28. Rubeosis iridis in one or both eyes.

29. Myopia of greater than 7 diopters in one or both eyes.

30. Chronic requirement for any ocular medication.

31. The inability to obtain adequate quality stereo fundus photographs.

32. Prior photocoagulation.

4.3.2 Exclusion Criteria for Subjects Without Retinopathy

The presence of diabetic retinopathy manifested by any one of the following lesions on central grading of stereo fundus photographs or clinical exam.

1. Microaneurysms
2. Hemorrhages
3. Hard exudate
4. Soft exudate

5. Intraretinal microvascular abnormalities (IRMA)
6. Venous caliber abnormalities
7. Arteriolar abnormalities
8. New blood vessels or fibrous proliferation
9. Vitreous or pre-retinal hemorrhage
10. Retinal edema

4.3.3 Additional Exclusion Criteria for Subjects With Minimal Background Retinopathy

The presence of diabetic retinopathy sufficient to categorize either eye as P2 or worse based on central grading of stereo fundus photographs.

Macular edema defined as definite thickening of the retina within one disc diameter of the center of the macula (even if the visual acuity is not yet reduced), as assessed by stereo fundus photography.

4.4 Recruitment

It is not necessary that individuals be referred to the study by a physician; subjects may refer themselves. Each subject must agree, however, that all diabetes care will be provided by the DCCT clinical center health care team.

A recruitment program will be initiated by the DCCT whereby each clinical center will employ recruitment strategies selected among various options best suited to that clinic. These strategies may include advertisement in the mass media of the trials need for volunteers.

5. INFORMED CONSENT

5.1 General Principles

In order to be eligible for the trial, each participant must be willing to sign a statement of informed consent prior to randomization. This will document the agreement of the subject to participate in the study activities. For subjects less than 18 years old, a parent or guardian must also sign the informed consent statement.

The basic elements of the informed consent are:

1. A straightforward statement that the study involves research and a clear explanation of the purpose of the trial, including a description of the procedures to be followed in the screening, eligibility determination, baseline and follow-up examinations as well as those procedures to be followed in the two treatment regimens, and the identification of experimental procedures, the method of treatment assignment, and the expected duration of the subjects participation.
2. A description of the outcome(s) of primary interest, the length and schedules of treatment and followup, and methods of locating and following up subject participants who transfer to inactive status.
3. A description of the attendant and reasonably foreseeable discomforts and risks, as well as a description of any reasonably expected benefits.
4. A disclosure of alternative procedures that might be advantageous for the subject.
5. A statement that participation is voluntary and the subject is free to refuse to participate or withdraw consent and to discontinue participation in the project or activity at any time without jeopardizing his/her medical care.
6. No exculpatory language through which the subject is made to waive, or appear to waive, any of his legal rights, or to release the institution or its agents from liability for negligence.
7. A description of the measures taken to ensure confidentiality of subject information.
8. A description of the measures taken to ensure subject safety.
9. An explanation of a subjects rights to compensation for research-related injuries and identification of specific individuals to contact regarding injury and/or questions related to rights as a research subject.
10. A description of subject responsibilities, including an explanation of the information that will be available during and at the conclusion of the trial.

11. An offer to answer all inquiries concerning participation in the research including identification of specific individuals to contact for answers to pertinent questions about the research.
12. A statement that participation in the study may involve risks which are currently unforeseeable.
13. An explanation of circumstances under which the subjects participation may be terminated by the investigator without regard to the subjects consent.
14. An explanation of the health consequences of a subjects decision to withdraw from the research and the need for orderly termination of participation.
15. A statement that significant new findings developed during the course of the study which may influence the subjects willingness to continue participation will be provided to the subject.

In accordance with DHHS policy on informed consent, it is necessary "to recognize that each subjects mental and emotional condition is important and that in discussing the element of risk a certain amount of discretion must be employed consistent with full disclosure of facts necessary to any informed .footnote consent."⁶

The Steering Committee recognizes that individual collaborating clinical centers may require that the recommended Informed Consent Form be amended to include additional statements or be reworded to clarify existing statements. All such modifications to the Informed Consent Form will be reviewed, and those which retain and do not detract from the content of the suggested DCCT Informed Consent Form will be approved. In addition, copies of signed Informed Consent Forms will be kept in a locked fire-proof safe in the Coordinating Center.

5.2 Sequence of Procedures

A two-stage informed consent procedure is part of a multi-level screening process. It is desirable that the Principal Investigator or the DCCT physician who will care for the subject be involved in the early stages of the sequence. The first Informed Consent Form obtains the subjects permission, and in the case of adolescents, the parents permission, for the eligibility tests to be performed.

The second Informed Consent Form obtains the subjects permission, and in the case of adolescents, the parents permission, to participate in the clinical trial.

The tools utilized for securing informed consent are the DCCT Recruitment Flyer, Volunteer Information Handbook, Manual of Diabetes Tests, Terms and Special Procedures, DCCT Slide Presentation, Volunteer Understanding Questionnaire, and Informed Consent Forms Numbers 1 and 2. Appendices A and B contain the Informed Consent Forms Numbers 1 and 2.

⁶ Salgo vs. Leland Stanford Jr. University Board of Trustees (154 C.A. 2nd 560; 317 p. 2-1701).

6. PRE-RANDOMIZATION EVALUATION

6.1 General Principles

After preliminary screening, at the time of the pre-randomization examinations, the prospective participant will be asked for written consent for the standardized history and physical examination and other eligibility evaluations. All examinations will be scheduled to coordinate with other pre-randomization requirements to optimize convenience for prospective study participants and to minimize cost by performing the least expensive tests, and those most likely to yield abnormal results, first (e.g., dipstick screen for urinary protein before microalbuminuria by radioimmunoassay). Table 6.1 illustrates a way of organizing the pre-randomization evaluations.

Although investigators have the flexibility to arrange the examinations in any order, strict rules (see the Manual of Operations) will be enforced regarding the repeated testing of ineligible subjects to prove them eligible.

6.2 Laboratory

The pre-randomization examinations include local clinical laboratory procedures which are given in Table 6.1. In addition, some specimens will be sent to the Central Biochemistry Laboratory for determination of eligibility criteria as well as to serve as baseline data.

6.3 Ophthalmologic

1. The pre-randomization ophthalmologic examination consists of the following standardized procedures:
2. Visual acuity
3. Intraocular pressure measurement
4. Slit-lamp and ophthalmoscopic examinations
4. Stereo fundus photography consisting of seven standard fields
5. Stereo fluorescein angiography in consenting subjects eligible for the primary prevention trial.

Original fundus photographs and angiograms will be sent to the Central Ophthalmologic Reading Unit for determination of photographic quality, subject eligibility, and baseline status.

6.4 Renal

The pre-randomization renal examination consists of the following standardized procedures:

1. Preliminary urine dipstick screen, urinalysis (UA) and urine culture (UC). If UC reveals 10^5 colonies per ml, a repeat culture is obtained. UC is mandatory in females and will be done for males when indicated by UA (2-4 WBC/hpf);
2. Microalbuminuria (four-hour timed collection)
3. Serum creatinine, albumin
4. Urine creatinine, albumin
5. Creatinine clearance
6. I-125 iothalamate clearance
7. Urine creatinine, sodium and urea nitrogen (24-hour urine collection)

Specimens will be sent to the Central Biochemistry Laboratory for determination of microalbuminuria, creatinine clearance, I-125 clearance, urine creatinine, sodium and urea nitrogen.

6.5 Neurologic

The pre-randomization neurologic examination consists of the following standardized procedures:

1. Neurological history and physical examination
2. Standing and supine blood pressures and pulse
3. Autonomic nervous system function tests
4. Nerve conduction studies

Autonomic Nervous System Function Tests will be centrally read at the Central Autonomic Coding Unit.

6.6 Cardiovascular

The pre-randomization cardiovascular examination consists of the following standardized procedures:

1. History and physical examination
2. Peripheral vascular history and physical examination (performed as part of the medical history and physical examination)
3. Resting EKG

EKGs will be interpreted locally for determination of subject eligibility and the results will be mailed to the Coordinating Center on standardized forms. EKGs determined to be abnormal on the basis of local reading may be sent to the Central EKG Reading Unit for confirmation. All EKGs on

eligible subjects will be mailed to the Central EKG Reading Unit for coding. These data will be sent to the Coordinating Center.

6.7 Psychological

The pre-randomization psychological assessment includes:

1. Neurobehavioral Assessment: A battery of neurobehavioral measures will be performed. The scope of the assessment includes: learning, memory, problem solving, and visuoperceptual and visuomotor functions. Performance results will be sent to the Central Neurobehavioral Coding Unit for scoring and coding.
2. Psychologic Symptoms: The Symptom Checklist-90-R will be completed.
3. Quality of Life: A questionnaire will be completed for evaluation of several areas including social functioning, work and school performance, attitudes toward diabetes and toward the specific demands of the DCCT Protocol. Age-specific and developmentally relevant inquiries are included.

6.8 Compliance/Adherence

The pre-randomization compliance/adherence assessment of the DCCT will consist of the following components:

1. Prospective subjects will be screened during a structured session in an effort to evaluate areas which are known to relate to adherence to Protocol requirements and compliance with prescribed regimens. A counseling-educational session with the subject and the family will be required to improve participation through a good understanding of trial procedures. Making use of written and audiovisual aids, a study representative will also discuss the following areas in detail with the subject and family:

- a) Expectations regarding the study
 - b) Mobility
 - c) Personal availability
 - d) Family and social supports
 - e) Past history of adherence to prescribed treatment for diabetes
 - f) Attitude about the study
2. Potential study subjects will be given behavioral tasks prior to randomization to evaluate compliance with regimens. These tasks will include skills training and assessment of behaviors which are relevant to the protocol of this trial, i.e., insulin injections, urine testing, glucose monitoring, and pump usage. All subjects will be placed on a regimen similar to standard treatment and will be asked to record, in a diary during a two-week period, a number of tasks to include eating habits, urine testing, time of injections, a 3:00 a.m. capillary blood collection.

6.9 Dietary

The pre-randomization dietary assessment consists of a diet history administered by the study dietitian and sent to the Central Nutrition Coding Unit for analysis.

6.10 Examination Results

All results of the preceding examinations will be collected on standardized forms and these will be mailed to the DCCT Coordinating Center. The timely submission of the screening, eligibility and baseline results is the responsibility of the individual clinical centers.

The centrally determined results are masked to the staff of the clinical centers. However, at the time such a result indicates a subject is permanently ineligible for the study, all eligibility and baseline results are released to the Principal Investigator and Trial Coordinator. .section Quality Control

Missing or technically inadequate measurements of any of the baseline variables described in this section (except the fluorescein angiograms and I-125 iothalamate studies) must be replaced before randomization will be permitted. Standards of technical adequacy are specified in the Manual of Operations.

Table 6.1
Screening, Eligibility and
Baseline Tests and Procedures

LOCAL SCREENING	ELIGIBILITY	BASELINE***
1) Initial contact	1) Laboratory** a) Blood Glucose Control HbA1c b) C-peptide (basal & stimulated) c) Fasting Cholesterol	1) Laboratory** a) Blood Glucose Control HbA1c Capillary blood glucose profile (CBG)
2) Presentation of Informed Consent Form on DCCT	2) Ophthalmic a) Visual acuity b) Intraocular pressure c) Slit-lamp and ophthalmoscopic exam d) Stereo fundus photographs**	b) Lipids Cholesterol Triglycerides HDL Calculated LDL
3) Consent #1 to undergo Eligibility Exams	3) Renal a) microalbuminuria by radioimmunoassay** b) Serum creatinine** (at investigator's discretion creatinine clearance may be done at this stage of the eligibility screen)	2) For subjects with less than or equal to 5 years duration of IDDM, ophthalmic fluorescein angiography** (if necessary another pregnancy test prior to angiography)
4) History and Physical Examination	4) Cardiovascular a) History and Physical (including blood b) Resting EKG	3) Renal a) Creatinine Clearance ** b) 24-hour urine collection c) I-125 iothalamate clearance
5) Local laboratory procedures* Hb electrophoresis CRC Mutichannel analysis of serum (including NA+ K+ CL- uric acid CA++ PO4— SGOT Alkaline Phosphatase total protein albumin cholesterol) Dipstick screen for urinary protein Serum creatinine Urinalysis Urine Culture (mandatory in females; in males only if indicated by specified abnormalities in urinalysis)	5) Adherence Assessment	4) Neurologic a) Standardized Symptom History & Physical Exam b) Autonomic Nervous System Function** (RR variation on ECG) c) Non-invasive nerve conduction study
14 TSH	6) Pregnancy Test	5) Psychological a) Full neurobehavioral assessment** b) Symptom Checklist-90-R (SCL-90-R) c) Quality of Life Questionnaire
	7) Volunteer's Understanding Questionnaire	6) Dietary – Diet history of past year**
	8) Consent #2 to participate in DCCT	7) Additional and sufficient blood will be drawn and stored in the CBI freezer for purpose of performing in the future assays which are not currently specified

* Local lab procedures are employed to document the general health of patient.

** Central lab or Central Reading Unit.

***Baseline occurs before randomization.

It is performed to obtain a reference point for each patient and not to exclude participants.

7. RANDOMIZATION

7.1 Phase II Randomization

During Phase II, 278 subjects were randomized to either the standard (S) or the experimental (E) treatment groups. In Phase II it was desired that the feasibility objectives be addressed separately for adults and adolescents. The Phase II randomization was conducted using the Urn randomization procedure (Wei, 1978) with stratification by adults and adolescents within each of the 21 Phase II clinical centers, 42 strata in all. Among the 278 subjects randomized into Phase II, 110 did not have any retinopathy, whereas 168 had minimal retinopathy on entry.

7.2 Phase III Randomization

7.2.1 Stratification

Based upon the results of Phase II it was decided that both adults and adolescents would be included in Phase III, but the objectives would not be addressed separately for adults and adolescents. The Phase III study will consist of two separate components, the primary prevention trial consisting of subjects with no retinopathy, and the secondary intervention trial consisting of subjects with minimal background retinopathy on entry. The Phase III randomization will be stratified both by clinic and retinopathy status, but not by age.

7.2.2 Randomization Sequences

The sample size objective for the total study (Phases II and III combined) is 1400 subjects, approximately 700 subjects in each of the primary prevention and secondary intervention trials. The 21 original Phase II clinics will be required to recruit approximately 1160 subjects, 580 in the primary prevention trial and 580 in the secondary intervention trial, including the Phase II subjects already recruited. Additional clinics will be expected to recruit a total of 240 subjects, 120 for each of the primary prevention and secondary intervention trials. For each of the clinics, the Coordinating Center prepared a sequence of random allocations for up to 50 subjects within each of the primary prevention and secondary intervention trials, 100 subjects total per clinic. This will allow for some clinics to recruit in excess of the target requirement to compensate for deficiencies, if any, in recruitment experience by other clinics.

The 278 Phase II subjects were post-stratified according to baseline retinopathy status within each clinic. For each clinic-retinopathy stratum, a separate randomization sequence was then constructed, which included the subjects already recruited in Phase II. Additional Phase III subjects are then randomized within clinic-retinopathy strata. The randomization sequence was generated using the Urn randomization procedure (Wei, 1978), using as the starting point the next allocation within each clinic-retinopathy stratum constructed from the Phase II subjects. In addition, randomization sequences were prepared for new clinics.

For large samples, the Urn procedure minimizes the potential for selection bias, i.e., minimizes the potential that the clinics may influence the assignment of treatments to subjects by

guessing which treatment will be assigned next. The Urn procedure, however, does not guarantee equal numbers of subjects in each treatment group. Rather, the probability of a substantial imbalance in the numbers assigned to each treatment is virtually eliminated by this procedure. Within either the primary prevention or secondary intervention trial, the probability that more than 370 of the 700 subjects would be assigned to either group is only 0.0073. The exact number of subjects to be randomized to either group is unknown because the exact number of subjects to be recruited within each clinic-retinopathy stratum is unknown.

7.2.3 Pace of Randomization

Each clinic is required to randomize subjects into both retinopathy strata. No clinic will be allowed to recruit and randomize significantly more of one type of subject than the other. It is not possible to predict the actual rate of randomization; therefore, when the randomization quota is met studywide for either retinopathy stratum, recruitment for that component will cease and full efforts will be concentrated on the other. Recruitment will continue for three years or until the full cohort for both strata has been met.

7.3 Mechanics of Randomization

The list of random assignments will be kept confidential and accessible only to the Coordinating Center staff at the time of randomization. Randomization into one of the two treatment groups will be accomplished by a telephone call to the Coordinating Center after all criteria for entry into the study have been satisfied and documented at the Coordinating Center. At the time of randomization, the next treatment assignment for that subjects clinic-retinopathy stratum is communicated by telephone to the treatment center staff, with written verification to follow. Each subject will then be included in the assigned treatment group in all statistical analyses regardless of the eventual therapeutic course. Thus subjects who fail to comply with or who are unable to complete the assigned treatment regimen will nevertheless be included in the originally assigned group for statistical analyses.

7.4 Ineligible Subjects Who Are Randomized

It is possible that there will be subjects who will be randomized who do not fully meet the eligibility criteria. This may arise either due to a deficiency in the eligibility screening of a subject or due to the initiation of changes in eligibility requirements which would then deem some previously randomized subjects to have been ineligible. Upon the detection of the ineligibility of a randomized subject, the Coordinating Center will inform the Principal Investigator. Such subjects will continue to be treated and managed according to the Protocol. Ineligible subjects who are randomized will be included in all statistical analyses of study outcome measures.

REFERENCES

Wei LJ. An application of an urn model to the design of sequential controlled trials. J Amer Stat Assn 73:559-563, 1978.

8. METABOLIC CONTROL

8.1 Intervention Strategy in the Standard Group

The standard treatment regimen is meant to approximate within the context of a clinical trial conventional, "non-intensive" treatment of IDDM as it is carried out in typical subjects by experienced health care teams, including those of the participating centers.

8.1.1 Intervention Strategy

The recommended intervention strategy for the standard group is defined in terms of two sets of aims.

First Priority: To achieve absence of symptoms attributable to glycosuria or hyperglycemia; absence of ketonuria; maintenance of normal growth and development and ideal body weight; and freedom from frequent or serious symptomatic hypoglycemia. Physician-investigators will be expected to intervene if any of the above first priority aims are not being met using their best judgment as physicians. Such intervention will take the form of dietary reinforcement or change of type and dose of insulin within the recommended limit of two injections per day and within the standard schedule of clinic visits and monitoring procedures described below.

Second Priority: Even if the first priority aims are being met, intervention will be required when the HbA1c exceeds two standard deviations above the mean value prevailing in insulin-dependent diabetic footnote populations.⁷ No intervention will be required if the first priority aims are being met and the HbA1c value is at or below the mean plus two standard deviation levels of current insulin-dependent diabetics (i.e., 13.11). No intervention will be permitted with the object of raising the HbA1c level solely for the purpose of this study.

In the standard group, HbA1c results will be routinely masked. HbA1c analyses will be done in the Central Biochemistry Laboratory (CBL) every three months. Within two weeks of the time the blood sample is obtained, all values below the upper action limit will be reported to the investigator as "within acceptable limits" in an individualized format that can be shown or sent to the subject. Values exceeding the upper action limit will be reported to the investigator within two weeks of the time the blood sample is obtained as an "Alert" mandating treatment change according to the Protocol. The actual HbA1c value will be provided when it exceeds the upper action limit, and repeat HbA1c analyses will thereafter be carried out as frequently as every month in the CBL until the value is brought below the upper action limit. No HbA1c assays are to be routinely carried out in the local laboratory. However, in the event of a marked discrepancy between the reported HbA1c and the clinical condition of the subject or the occurrence of a major intercurrent event which, in the investigators judgment necessitates an interim HbA1c analysis, an additional sample should be promptly sent to the CBL. At the same time, if deemed necessary by the investigator, an interim HbA1c may be obtained at a local laboratory on an urgent basis.

⁷ This mean value, as determined from the Phase II Central Hemoglobin A1c Laboratory's measurement of 205 blood specimens from a random sample of IDDM subjects from the 21 original participating clinical centers is 8.95 with a standard deviation of 2.08, using pre-incubated samples and a high performance liquid chromatograph (HPLC) technique. The upper action limit is 13.11.

8.1.2 Insulin

Insulin will be administered as one or two injections per day. Mixtures of short-acting, intermediate-acting, and/or long-acting insulin may be employed as needed. Pork, mixed beef/pork, or human insulin may be employed.

8.1.3 Diet

An individualized meal plan which provides for the total nutritional needs of the subject will be an integral part of the treatment regimen. The meal plan will be quantitative in nature with individualization of amounts of food and of identifiable times of food consumption. The meal plan will be compatible with the remainder of the therapeutic regimen, e.g., with the insulin schedule and exercise patterns.

The meal plan will be designed to promote normal growth and development in adolescents and maintain ideal body weight in adults. It should be adaptable to the individual subjects needs with regard to cost, food availability, beliefs, cultural influences, particular tastes, and educational background. The American Diabetes Associations prudent fat diet employing exchange lists is a suitable basis for the initial dietary prescription on entry into the study, but it may be modified as necessary. Reinforcement of the dietary program will be carried out by the dietitian every six months.

In subjects with persistent hypercholesterolemia (see Manual of Operations for a definition) the prescribed cholesterol content of the diet will be lowered to less than 300 mg/day with a polyunsaturated to saturated fat ratio of approximately 1.0, and no more than 10% of calories as saturated fat. The diet will be modified when necessary to meet the requirements of other medical conditions.

8.1.4 Exercise

Specific exercise prescriptions are not required. Exercise will be encouraged according to the individuals interests and physical fitness. Scrupulous adjustment of insulin delivery and diet to the exercise pattern will be emphasized to ensure safety.

8.1.5 Self Monitoring/Glucose

Effective July 1, 1988

The volunteer will be expected to monitor his/her diabetes on a regular basis. All patients will be taught urine glucose testing and self monitoring of blood glucose (SMBG). The patients may choose to perform urine glucose testing two to four times per day, SMBG once a day, or a combination of both methods. Routine SMBG more than once a day should be recommended only if the patient fails to meet the first or secondary priority treatment goals of the Standard Regimen, i.e., absence of ketonuria, maintenance of normal growth and development and ideal body weight, freedom from frequent or severe hypoglycemia and maintenance of hemoglobin A1c less than 13.11%. Neither urine nor blood glucose tests are for the purpose of achieving any specified day-to-day numerical targets. Rather these tests are for the purpose of alerting the patient and clinic staff to unrecognized or unacknowledged symptoms of hypoglycemia or

hyperglycemia and to the necessity of testing urine ketones when urine glucose is consistently greater than 2% or blood glucose is consistently greater than 240 mg/dl. SMBG may be the preferred method for managing sick days or providing guidelines for adjustment of treatment during exercise. However, SMBG should not be used by patient or Clinic staff for the express purpose of lowering blood glucose or hemoglobin A1c when first and second priority treatment aims are already being met.

8.1.6 Self Monitoring/Ketone

Subjects will be asked to measure urine for acetone if the urine glucose is 2 gm/dl or greater, capillary blood glucose is repeatedly greater than 240 mg/dl, or with intercurrent illness.

8.1.7 Clinic Visits

Subjects in the standard treatment group will be seen at three-month intervals and will be assessed by: history, emphasizing symptoms of glycosuria; physical examination, with particular emphasis on growth in adolescents; review of subject-recorded tests, a blood sample drawn for CBL analysis of HbA1c; and, at the discretion of the investigator, a plasma glucose determined at the local laboratory. In addition, a self blood glucose collection consisting of seven samples will be analyzed at the CBL for study purposes.

8.1.8 Educational Program

An educational program will be provided to ensure that a complete cycle of the subject matter is covered every two years (hygiene, foot care, urine testing, injection techniques, insulin reactions, management of intercurrent illness, etc.). The educational program will also include reinforcement of participation in the clinical trial.

8.1.9 Protection of Subjects

In the event that a subject in the standard group cannot be successfully managed by the intervention strategy outlined above, i.e., persistently fails to meet either a first or second priority aim, then the investigator must modify the standard regimen. Such modifications may include the use of more frequent subject-staff out-patient contact, more intensive dietary instruction, and hospitalization for metabolic control. These modifications will be reviewed by the Treatment Committee. If more than two injections or an insulin pump is considered necessary to achieve first and second priority aims, prior permission of the Treatment Committee must be obtained. So long as any modification is only for the purpose of achieving the first and second priority aims in Section 8.1.1, it will not constitute a deviation from the standard treatment protocol (see Section 12.3 for the definition of deviation from the standard treatment protocol).

8.2 Intervention Strategy in the Experimental Group

The experimental treatment regimen is designed to achieve and maintain control of blood glucose as near normal as possible in the absence of significant hypoglycemia. Therefore, in

addition to meeting the criteria stipulated for the standard regimen, the intensity of treatment in the experimental regimen is directed toward specific additional targets.

8.2.1 General Guidelines

Aims: The aim in the Experimental Treatment Group is to achieve and maintain as near normal glycemic control as possible in the absence of significant hypoglycemia.

For Blood Glucose:

Fasting and preprandial levels: 70-120 mg/dl
Postprandial levels:
less than 180 mg/dl (90-120 minutes after meal)
3:00 a.m.: 65 mg/dl or above

For HbA1c: The goal will be to maintain the HbA1c level within two standard deviations of the mean for a sample of persons without diabetes.⁸

In the experimental group, HbA1c values will be unmasked. The required monthly HbA1c analysis will be done in the Central Biochemistry Laboratory, and the individual values will be reported to the investigator within two weeks of the time the blood sample is obtained. No routine HbA1c assays may be performed in the local laboratory.

For Hypoglycemia: The goal will be no episodes of hypoglycemia which require treatment by persons other than the subject; no episodes associated with altered mental status, even if they can be managed by the subject without assistance; fewer than four episodes per week without significant mental impairment and easily self-treated.

8.2.2 Insulin

Intensive insulin delivery will be carried out in one of two ways:

Insulin may be delivered by continuous subcutaneous infusion employing a pump and consisting of a basal infusion rate coupled with preprandial doses (pump, CSII).

Insulin may be administered as three or more subcutaneous injections of insulin daily (MDI).

Pork, mixed beef/pork, or human insulin may be employed.

The choice of insulin delivery method shall rest with the DCCT physician and the individual subject. Either pump or MDI may be tried first and the alternate method employed if treatment goals are not met. For purposes of data analysis, subjects treated by pump only, subjects treated

⁸ This mean value, as determined from the Phase II Central Hemoglobin A1c Laboratory's measurement of 124 blood specimens from a random sample of non-diabetic subjects from the 21 original participating clinical centers, is 5.05 with a standard deviation of 0.50, using pre-incubated samples and a high performance liquid chromatograph technique. The upper action limit is 6.05.

by MDI only, and subjects treated by both pump and MDI will constitute a single group whose outcomes will be compared to those of the Standard Treatment Group. The details of the Pump Treatment Protocol and the MDI Treatment Protocol are given in the Manual of Operations.

8.2.3 Diet

The same principles of dietary management will be followed as outlined in the intervention strategy for the Standard Treatment Group. In addition, however, it may be anticipated that some subjects in the Experimental Treatment Group will modify their dietary plan themselves by experience. Such self-modifications may be permitted as long as the subject adjusts insulin accordingly and intelligently and as long as standards for good nutrition are being met. Reinforcement of the dietary program will be carried out by the dietitian as often as necessary to attain experimental treatment goals.

8.2.4 Exercise

Specific exercise prescriptions are not required. Exercise will be encouraged according to the individuals interest and physical fitness. Scrupulous adjustment of insulin delivery and diet to the exercise pattern will be emphasized to ensure safety.

8.2.5 Monitoring/Ketones

Self blood glucose monitoring is the mandatory form of monitoring diabetes in this group. Urine test for ketones will be required when the blood glucose exceeds 240 mg/dl or an intercurrent illness develops. Other urine tests for glucose and ketones may be obtained at the discretion of the investigator to supplement, but not substitute for, blood glucose measurement.

8.2.6 Blood Glucose Monitoring

Self blood glucose monitoring will be performed a minimum of four times a day, to include three preprandial and one bedtime sample. A 3:00 a.m. sample will be obtained once a week. If the value is less than 65 mg/dl, the subject will repeat the 3:00 a.m. sample the next night. The clinic staff is to be notified promptly if the repeat value is also less than 65 mg/dl. Postprandial samples for self monitoring will be obtained at least every three months concurrent with collection of the home capillary blood samples for central data analysis (Section 9.1). In the event that the intervention aims are not being met, more frequent self monitoring of pre- and postprandial glucose profiles will be required. Subjects may also be asked to bring blood glucose samples collected at home for analysis in a local laboratory in order to validate the accuracy of subject reports. For measurements of blood glucose performed at home, the use of a reflectance meter is required. For measurements of blood glucose performed away from home, the use of visually determined estimates is permitted.

8.2.7 Clinic Contacts

Subjects will be seen weekly until the desired treatment goals have been achieved and at least monthly thereafter. Each center will have a system for ready availability of professional staff possibly including occasional nighttime or weekend clinics. Telephone contacts will be made daily for the first week, then weekly thereafter.

8.2.8 Protection of Subjects

If intensification of treatment for the purpose of achieving the experimental group HbA1c goal results in repeated severe hypoglycemia that cannot be prevented by adjusting insulin dose or mode of delivery, diet, exercise, or subject reeducation, then the blood glucose and HbA^{1c} targets must be raised to a level consistent with subject safety. This is considered a modification of the experimental treatment regimen and as such will be reviewed by the Treatment Committee.

8.3 General Procedures to Maximize Adherence to Protocol

The hypothesis of the DCCT will be explained as thoroughly and frankly as possible. The subject will be recruited into a research alliance with the investigator. The equal importance of participating in the Standard or the Experimental Treatment Group will be emphasized before informed consent is sought and reemphasized periodically thereafter. The positive aspects of participating in the DCCT will be emphasized. These include regular and sophisticated surveillance for complications, early stop points, and rapid transfer of results to subjects regarding whichever (if either) treatment protocol proves to be superior with regard to the development or progression of complications.

One person will be clearly identified in each of the professional disciplines (physician, nurse-clinician, dietitian, consultants) who will primarily relate to the subject in his or her area of diabetes management. A backup individual for coverage when the primary care giver is not available will also be identified. Alternate professionals should be identified and periodically introduced. As much as possible, equalization of secondary health care benefits in the Standard and Experimental Treatment Groups should be practiced.

Periodic structured group meetings will be held to provide feedback from the DCCT to the subjects and to encourage the latter to voice questions, concerns, or suggestions regarding the trial. All DCCT subject activities will be conducted with the utmost courtesy, convenience, efficiency, brevity, and openness. Transportation, parking, maintenance of meal patterns, child care, etc., will all be facilitated whenever possible. Of necessity, this will be dependent upon local resources available to the investigators.

9. PROCEDURES FOR FOLLOW-UP VISITS

9.1 General Principles

During the course of the study, participants will be asked to undergo a set of regularly scheduled standardized procedures for subject followup. All visits will be scheduled to coordinate these procedures and examinations with other requirements in order to optimize convenience for the study participants and to minimize costs. Additional visits may be scheduled as necessary for the clinical care of the subject.

A standardized follow-up history and physical examination will be scheduled yearly for each subject. In addition, urinalysis, urine culture, and hemoglobin are performed and assayed locally. The schedule for other follow-up procedures is discussed in the following sections.

9.2 Blood Glucose Control

Measurements will be conducted at the Central Biochemistry Laboratory for the purpose of data analysis and will include the following tests and schedules:

1. HbA1c to be assayed in the Central Biochemistry Laboratory.
2. Collection of blood samples from the quarterly home blood glucose profiles to be analyzed at the Central Biochemistry Laboratory. In addition, in the experimental group, recorded results of self blood glucose monitoring corresponding to samples collected for blood glucose profile.
3. Recorded average number of self blood glucose determinations per week in experimental group.
4. Recorded 3:00 a.m. blood glucose results in the experimental group.
5. Recorded daily insulin dosages: total, basal, and preprandial boluses for experimental group; total rapid acting, and intermediate or long acting for standard group.

9.3 Ophthalmologic

Examination schedules for routine followup and procedures during Phase III are the same for all subjects: baseline and every six months thereafter.

Original fundus photographs and angiograms will be sent to the Central Ophthalmologic Reading Unit for analysis. Copies of the photographs and angiograms will be maintained at the clinical centers.

There will be two different examination routines. Stereo fundus photography will be performed at baseline and every six months thereafter. The yearly examination includes the following additional procedures:

6. Visual acuity;
7. Intraocular pressure measurement;
8. Slit-lamp and ophthalmoscopic examinations.

Fluorescein angiography, performed at baseline only in primary prevention subjects, will be repeated at five years and study termination in these subjects and possibly at other intervals if indicated.

9.4 Renal

Renal examination will be performed at the annual visit. Urinalysis (UA) will be done in conjunction with the annual history and physical examination. Urine culture (UC) will be done on all females and on any male if an abnormal urinalysis is indicated. The UA and UC will be analyzed locally. Annually, urine and serum will be sent to the Central Biochemistry Laboratory for the following:

1. Microalbuminuria (in-clinic four-hour timed collection);
2. Serum albumin;
3. Creatinine clearance;
4. Serum creatinine.

At three years and/or study termination, an I-125 iothalamate clearance will be done simultaneously with the four-hour timed collection for microalbuminuria.

9.5 Neurologic

The following procedures will be performed every second year:

5. Standing and supine blood pressures and pulse;
6. Autonomic nervous system function tests (RR-variation on EKG).

Update of the neurologic history and physical examination and nerve conduction studies will be performed at five years and/or study termination.

The autonomic nervous system function tests (RR-Variation on EKG) will be centrally read at the Central Autonomic Coding Unit.

9.6 Cardiovascular

Cardiovascular follow-up examinations will consist of the following:

7. A standardized follow-up history and physical examination for peripheral vascular disease performed yearly;
8. Triglycerides, total cholesterol, and high density lipoprotein cholesterol measured annually on serum collected after an overnight fast and analyzed by the Central Biochemistry Laboratory (low density lipoprotein cholesterol will be calculated from the above measurements);
9. Resting EKGs every two years coded at the Central EKG Reading Unit.

9.7 Psychological

Effective July 1, 1988

The following psychological assessments will be made during the course of the trial:

10. Neurobehavioral Assessment: The full battery, performed initially at baseline, will be repeated at year two, year five, year seven and at study termination, if it has been longer than one year since the last assessment. Performance results will be sent to the Central Neurobehavioral Coding Unit for scoring and coding.
11. Psychologic Symptoms: The SCL-90-R will be completed yearly.
12. Quality of Life: The Quality of Life Questionnaire will be completed yearly.

9.8 Compliance/Adherence

The post-randomization compliance/adherence program will be accomplished through the implementation of such strategies as participant counseling, encouragement of peer and social supports, periodic educational programs, regular meetings, and newsletters. Guidelines for these strategies are presented in the Manual of Operations.

9.9 Dietary

The baseline, second year and fifth year and/or termination visit will include a diet history which will be sent to the Central Nutrition Coding Unit for analysis.

9.10 Examination Results

All the results of the preceding examinations will be recorded on standardized forms and mailed to the DCCT Coordinating Center. The timely submission of results of all examinations is the responsibility of the individual clinical center.

9.11 Missed Visits

The importance of the visit schedule will be stressed both to the subject and the staff of the clinical center. Ideally, no visits should be missed; however, if a visit is missed, the visit should be rescheduled as soon as possible. Specific time windows have been established and are given in the Manual of Operations.

9.12 Transfer

Every effort will be made to follow all study subjects according to the treatment regimens specified in the Protocol even when they make temporary or permanent moves to another city or section of North America.

When a subject moves into a geographic area served by a DCCT clinical center other than the one in which he/she was originally enrolled or is currently being served, the subject will be reassigned to the care of the new center. When a subject moves to an area not served by one of the DCCT clinical centers, subject management will have to be provided on a local basis. The staff of the DCCT clinical center will assist the subject in locating a physician willing to provide the appropriate treatment regimen, standard or experimental, according to the Protocol. Regular communication (monthly) should be maintained between the Principal Investigator and the local physician. Regular direct communication between the DCCT center and the subject should be maintained by telephone, letter, newsletter, and other adherence techniques.

All outcome measurements should continue to be performed at the subjects "home" center or the nearest DCCT center. This is particularly vital for fundus photography, the key outcome measurement. Fundus photographs should not be obtained by non-DCCT photographers, even if the latter have participated in other retinopathy studies. Every effort should be made for experimental subjects to continue to have monthly HbA1c and standard subjects quarterly HbA1c samples drawn and properly shipped to the Central Biochemistry Laboratory.

All subjects who transfer will continue in the treatment group to which they were originally randomized. The transfer of clinical care will be made with the fully-informed consent of the subject.

10. INTERNAL MONITORING

10.1 General Principles

Mechanisms have been instituted for continuous performance monitoring of all DCCT study units by the Study Group. External quality control surveillance has been instituted by the DCCT to assess the precision of all measurements made by the Central Biochemistry Laboratory (CBL), Central Ophthalmologic Reading Unit (CORU), and other central units. In addition, the performance of these units, the clinical centers and the Coordinating Center has been monitored through site visits and appropriate tabulations of indices of performance. These tabulations have been reported periodically to the appropriate study committee, and to the individual study unit, and to the Data, Safety, and Quality Review Group (DSQ) (see Chapter 17).

10.2 Responsibility for Monitoring

1. Performance monitoring of each study unit will be conducted by working committees of the Study Group. The Coordinating Center will participate in monitoring all study units by preparing tabulations of performance indices, by participating in site visits, and by maintaining permanent records of the performance of each study unit. Responsibilities of the working committees are as follows:
 - a) Standards/Methods Committee
 13. 1. Central Biochemistry Laboratory
 14. 2. Central Nutrition Coding Unit
 - b) Complications Committee
 - i) Central Ophthalmologic Reading Unit
 - ii) Central EKG Reading Unit
 - iii) Central Autonomic Coding Unit
 - iv) Central Neurobehavioral Coding Unit
 - c) Clinic Monitoring Group -- Clinical Centers
2. The NIDDK has appointed an independent group to review the performance of all study components to ensure the continued timeliness, quality of study data, and safety of subjects entered into the trial (see Chapter 17).

10.3 Performance Monitoring

10.3.1 Clinical Centers

All aspects of clinical center performance will be monitored regularly by the Clinic Monitoring Group (CMG). In particular, the CMG will monitor success of recruitment, adherence to treatment and follow-up schedules, standardization of study procedures, success in meeting treatment goals, and the occurrence of adverse effects of treatment, as allowed by required masking of outcome data. Review of performance data shall be conducted with sufficient frequency to allow timely detection of deviations from expected performance. Such deviations shall be investigated by the CMG and corrective actions recommended to the clinical center. Monitoring shall also include site visits conducted at appropriate intervals. If discussions between the CMG and the clinical center do not lead to improved performance, the CMG may recommend other actions to the DCCT Steering Committee.

Each central unit has established mechanisms by which the standardization of procedures performed by the individual clinical centers can be assessed and monitored. These will be reviewed periodically by the CMG.

10.3.2 Central Units

Central Biochemistry Laboratory

External quality control surveillance programs have been established to monitor the performance of the CBL. This will entail the masked submission of duplicate specimens from the clinics for analysis by the laboratory. The resulting data will allow an assessment of the on-going precision of the laboratory test results. Bench quality control assessment, though useful, will be inadequate because laboratory performance alone is but one step in a chain of activities that could influence the test results. A program of external duplicate surveillance will allow assessment of the total system starting with the collection of a specimen in the clinic and ending with the entry of the data into the Coordinating Center computer. The duplicate quality control data are analyzed periodically by the Coordinating Center and presented to the Standards/Methods Committee for review. Any deficiencies detected will be investigated and corrected.

Because of the critical nature of hemoglobin A1c data and the lack of an adequate external standard for this assay, special measures are needed to ensure precision over time under all circumstances. Therefore, a backup hemoglobin A1c laboratory has been established. Split duplicate aliquots of subject specimens are analyzed in both laboratories and the comparability of results assessed.

Central Ophthalmologic Reading Unit

Likewise, an external quality control surveillance program has been established for the CORU which entails the duplicate masked evaluation of fundus photographs. These data are analyzed periodically by the Coordinating Center and presented to the Complications Committee for review. Any deficiencies detected will be investigated and corrected.

Other Central Units

To the extent that other evaluations are standardized or are conducted in part by a central facility, comparable mechanisms for quality control surveillance will be initiated.

10.3.3 Coordinating Center

A specially constituted subcommittee of the DSQ (see Chapter 17) will site visit the Coordinating Center periodically to review procedures.

10.4 Correction of Deficiencies

If monitoring procedures detect deficiency in the performance of any study unit, the matter will be investigated by the appropriate working committee and then considered by the Executive Committee and/or Steering Committee. Expert consultants will be used as necessary. Steps will then be instituted to correct the deficiency. If, after a reasonable period, deficient performance persists, the matter will be referred to the NIDDK.

11. INTERCURRENT EVENTS

11.1 Definition of Intercurrent Events

Intercurrent events are occurrences (illnesses, accidents, etc.) which impact on, or are related to subject safety, treatment efficacy, or other study relevant conditions. The Manual of Operations identifies and defines specific intercurrent events to be reported and in some instances, outlines their treatment.

11.2 General Principles

Participation in the DCCT trial will in no way jeopardize the provision of appropriate treatment for intercurrent illnesses. Although specifics for the management of all possible intercurrent illnesses cannot be realistically set forth, the highest standard of care will be followed and liberal use will be made of appropriate consultants.

Subjects will be encouraged to contact the DCCT clinical center at the onset of symptoms suggesting any intercurrent illness. In addition, a 24-hour on-call system will be available to respond to all types of subject emergencies. Whenever possible, intercurrent illnesses requiring hospitalization will be managed at the DCCT clinical center with active involvement by the DCCT physician responsible for the subjects diabetes care. This will enable the study protocol to be followed as closely as possible without compromising treatment of the intercurrent illness.

11.3 Guidelines for the Management of Intercurrent Events

The DCCT Manual of Operations sets forth the diagnostic criteria and where appropriate the detailed guidelines for the management of the intercurrent events.

12. CHANGES IN TREATMENT

12.1 Introduction

In addition to intercurrent illness, other conditions may arise which could necessitate changes in the treatment protocols. In some situations, prolonged transfer to inactive status may also be unavoidable.

12.2 Modification of the Experimental Treatment Protocol

Inability to prevent or manage recurrent severe hypoglycemia, major sequelae of hypoglycemia (brain damage, sociopath behavior, myocardial infarction) or inability of the subject to detect the warning symptoms of hypoglycemia prior to the onset of cerebral impairment will require modification of the experimental treatment protocol. Other situations that may require modification of the treatment protocol are listed in Chapter 11 of the Manual of Operations. Depending on individual circumstances, the degree to which the goals of blood glucose control in an experimental group subject must be modified will vary. The greater the risk of or from serious hypoglycemia or the less the subjects ability or willingness to adhere to the experimental treatment protocol, the more the goals of the experimental protocol may need to be modified. However, the DCCT staff should always attempt to achieve a degree of control as close to the experimental treatment goals as can be safely and reasonably implemented.

In the event that a subject insists on deviation from the experimental treatment protocol, the investigator will discontinue the use of those treatment techniques to which the subject objects. However, with the subjects concurrence, the DCCT staff will continue to strive for the blood glucose and HbA1c goals of the experimental treatment with whatever techniques remain available to them.

12.3 Modification of the Standard Treatment Protocol

Modification of the standard treatment protocol will be required in the event of pregnancy or intention to conceive, as outlined in the Manual of Operations.

Should a subject otherwise insist on a program of management more stringent than that of the standard treatment regimen, the following is recommended. Each investigator will determine, on an individual basis, whether it would be in the best interest of the subject for that investigator to continue personal management of the subjects blood glucose control in this circumstance. If the investigator elects to continue such management personally, he/she will determine, with the subject, the techniques to be used and the blood glucose and/or HbA1c target levels to be sought. If the investigator elects not to continue such management personally, he/she will assist the subject in obtaining, from another physician, the type of blood glucose control desired by the subject.

In either case, the DCCT will continue to provide the same monitoring of clinical status and HbA1c levels and the same surveillance for microvascular and macrovascular complications. If another physician has assumed management of blood glucose control, that physician will be notified promptly of any change in retinopathy, in renal function, or in other outcomes that might warrant intervention according to DCCT policy.

12.4 Review of Modifications

Modifications of the treatment regimens will be reviewed by the Treatment Committee. If any particular modification is widespread, a change in the treatment protocol may be considered by the Treatment Committee.

12.5 Deviation from Treatment Protocols

1. Deviation from the experimental treatment protocol is defined as withdrawal from the intensive methods of insulin delivery set forth in Section 8.2.2.
2. Deviation from the standard treatment protocol is defined as institution of insulin delivery by pump or multiple daily injections for any purpose other than meeting the first and second treatment priorities set forth in Section 8.1.1.

12.6 Review of Deviations

Regarding any deviations or planned deviations, the Principal Investigator should call the Chairman of the Treatment Committee to discuss the specific situation. Deviations from the treatment regimen will be reported promptly to the Coordinating Center. The Clinic Monitoring Group will review the effect of the deviation on HbA1c. The Treatment Committee will be apprised of the number of deviations and reasons for them.

12.7 Transfer to Inactive Status

Transfer to inactive status is defined as a temporary or permanent moratorium on subject participation in the study to any extent whatsoever. Transfer to inactive status is allowable in the following situations:

1. When in the judgment of the Principal Investigator and mental health consultants, any manner of participation in the study could no longer be considered informed or would be directly injurious to the subjects well-being.
2. Catastrophic injury or illness resulting in coma, dementia, blindness, or inability to monitor diabetic retinopathy adequately.
3. Complete inaccessibility to metabolic management or to monitoring of endpoints (for example, long-term imprisonment).
4. Subject withdraws consent for continued participation in the trial.

12.8 Review of Transfer to Inactive Status

The Principal Investigator should discuss the application for transfer to inactive status with the Chairman of the Clinic Monitoring Group. Application for transfer to inactive status will be promptly forwarded to the Coordinating Center. The Clinic Monitoring Group will review the effect of transfers to inactive status. The Treatment Committee will review the number of transfers to inactive status and reasons for them.

13. RESULTS AND STATISTICAL ANALYSES

13.1 General Principles

The objectives of the DCCT described in Section 2 will be assessed through statistical analyses of those measurements and events described below. For the primary prevention study, these are the incidence of new cases of retinopathy, neuropathy or nephropathy. For the secondary intervention study, these are the incidence of progression of retinopathy, and development or progression of neuropathy or nephropathy. Also, these include measurements of level and variability of blood glucose control, the frequency of clinically significant events, measures of overall subject adherence to followup, and the precision and accuracy of study measurements.

13.2 Baseline Results and Analyses

The DCCT subject group is not a random sample from the general population of individuals with IDDM. It is a selected group of persons with diabetes who are sufficiently motivated to be involved in a long-term study and who have satisfied a comprehensive set of admissibility criteria. The distributions of the baseline variables among the combined treatment groups will serve as a detailed description of these characteristics for the group of subjects enrolled into the study.

13.3 Outcome Variables

To address the DCCT objectives, the following outcome measures will be employed in various statistical analyses to determine whether statistically significant and clinically meaningful differences exist between the treatment regimens.

Principal DCCT Objectives

1. Onset or progression of retinopathy
 - a) Primary Prevention Trial. The outcome variable which is the basis for the design of the primary prevention trial is the development of persistent diabetic retinopathy in individuals with no evidence of retinopathy on the detailed grading of the entry fundus photographs. Diabetic retinopathy is defined as the presence of at least one microaneurysm in either eye. The clinical significance of a treatment group difference for this outcome variable will be evaluated in consideration of trends at higher levels of retinopathy as defined by the DCCT index of retinopathy.
 - b) Secondary Intervention Trial. The outcome variable which is the basis for the design of the secondary prevention trial is the definite worsening of retinopathy in individuals who had mild to moderate nonproliferative diabetic retinopathy on the detailed grading of entry fundus photographs. A reliably detectable worsening in retinopathy is defined as a progression of three or more steps on the DCCT index of retinopathy. The clinical significance of a treatment group difference for this outcome variable will be evaluated in consideration of the proportions in each treatment group with proliferative diabetic retinopathy in either eye, DRS high risk

characteristics in either eye, clinically significant macular edema in either eye, and any retinopathy in either eye for which the patient received photocoagulation treatment.

2. Adverse Events

- a) Death
- b) Episodes of severe hypoglycemia.
- c) Episodes of diabetic ketoacidosis.
- d) Inability to maintain normal growth and development.
- e) Inability to maintain acceptable body weight.
- f) Inability to maintain psychological well-being.
- g) Neuropsychological evidence of cerebral dysfunction

Other Objectives

1. Onset of nephropathy

- a) The development of persistent albuminuria.
- b) The development of persistent renal insufficiency.

2. Onset or progression of neuropathy

- a) Among subjects free of any neuropathy on entry, the development of definite clinically evident peripheral neuropathy based upon the standardized examination.
- b) Among subjects with minimal neuropathy on entry, the definite worsening of clinically evident peripheral neuropathy based upon the standardized examination.

3. Incidence of cardiovascular events as defined in the Manual of Operations: The occurrence of at least one of the following:

- a) Major events:
 - i) Myocardial infarction.
 - ii) Significant ventricular arrhythmia documented by EKG.
 - iii) Diagnosis of congestive heart failure.
 - iv) Definite cerebrovascular accident.
 - v) Transient ischemic attack.

- b) Minor events:
 - i) Hypertension.
 - ii) Development of severe lipid abnormality associated with increased cardiovascular risk.

Operational Outcomes

1. Recruitment: Ability to recruit the full cohort of subjects within the specified time.
2. Glucose control: Maintenance of a difference between experimental and standard treatment groups.
 - a) HbA1c
 - b) Capillary blood glucose profile.
3. Individual subject management.
 - a) Occurrence of severe hypoglycemia.
 - b) Incidence of HbA1c greater than 13.11.
4. Adherence
 - a) Transfer to inactive status.
 - b) Deviation from the treatment protocol.
 - c) Missed visits
5. Precision and accuracy
 - a) HbA1c
 - i) Coefficient of reliability from external quality control.
 - ii) Laboratory variability measured by between-run coefficient of variation.
 - iii) Agreement with backup Hemoglobin A1c laboratory.
 - b) Capillary blood glucose profile. .
 - i) Coefficient of reliability from external quality control.
 - c) Stereo fundus photographs.
 - i) >80% agreement between repeated gradings of randomly selected photographs. .point end

13.4 Analysis Plan

All statistical analyses will be based upon the total cohort of subjects randomized into the trial. Although data on some subjects may be missing at points in time, all relevant data available from each subject will be employed in all analyses.

In all analyses, all subjects will be included in the group to which they were initially randomly assigned and group assignment will not be altered based on the subjects adherence to the assigned treatment program. Thus, subjects who deviate or transfer to the alternate treatment will be included in the initial randomly assigned group for statistical analysis.

Analyses of each outcome will include preliminary tests for interaction between clinic strata and treatment group in their effects upon the outcome variable. If an interaction is detected, additional analyses of that variable will be conducted with stratification by clinic. The analysis will be performed separately for the primary prevention and secondary intervention studies.

Differences between the groups in their baseline characteristics could bias the comparison of the treatment groups. Likewise, differences between the groups in the baseline characteristics of the subjects who later exit from the study could bias the comparison of the treatment groups on outcomes measured only in the subjects remaining in the study. If such differences in baseline characteristics are observed, analyses will also be conducted of the effects of the treatments on outcomes adjusting for the potential confounding effects of these baseline characteristics. If only a few such baseline characteristics are identified, analyses will be conducted stratifying for those characteristics. If, however, any more than a few baseline characteristics are identified, because of paucity of data, it will be necessary that regression models be employed to adjust the treatment comparison for the confounding effects of those characteristics.

Likewise, stratified analyses will be conducted adjusting for the effects of age, duration of IDDM and other known prognostic variables, and such variables will also be used in regression models to adjust the treatment comparison.

Intercurrent events such as death, major accident, myocardial infarction, cerebrovascular accident with persistent neurological deficit, non-traumatic amputation, loss of vision, renal insufficiency and neuropathy, as defined in the Manual of Operations will be reviewed and classified by an independent committee -- Morbidity/Mortality Classification Committee. (See Section 17.3 for a description of this Committee.) The results of this classification will be the bases for the statistical analyses of intercurrent events.

13.5 Interim Analyses

The interim analyses are intended to assess patient safety, Protocol integrity and data quality, and to determine whether the study objectives (Section 2.1) have been met. The DSQ (see Section 17) will meet regularly during the conduct of the study to monitor the emerging results and to assess the risks and benefits of each mode of therapy, thus insuring the safety of the subjects enrolled in the study. Statistical analyses will be conducted of all outcome variables for review by the DSQ prior to each meeting of the committee. These analyses will be conducted recognizing the effects of repeated statistical tests whereby the nominal Type I Error level increases after each such examination of the data. Plans for these interim statistical analyses and the statistical

methods to be employed will be specified by the DSQ and will be documented in a separate document entitled "Operating Procedures for the DSQ."

The interim analyses will include all outcome variables defined in Section 13.3. The DSQ will recommend modification of the Protocol or early termination of the study if differences are found between the treatment groups which are statistically significant and are deemed clinically important.

14. PUBLICATIONS AND PRESENTATIONS

14.1 Introduction

During the planning or conduct of the DCCT, there will be no effort to publicize study plans or results which have not been reviewed and approved by the participants. The Publications and Presentations Committee will coordinate, monitor, review and assume responsibility for arranging the preparation of all press releases, interviews, presentations, and publications relating to the DCCT. Recommendations will be presented to the Executive or Steering Committee of the DCCT for approval. Copies of approved material will be provided promptly to the NIDDK.

14.2 Duties of the Publications and Presentations Committee

Specifically, the Committee shall:

3. Recommend policy and procedures for review and approval of all communications regarding the DCCT to outside groups.
4. Identify publications to be written during the course of the study, with target dates for each.
5. Propose policy guidelines for authorship of DCCT publications, and/or recommend to the Steering Committee senior authors and co-authors for each paper.
6. Monitor the writing of each paper to ensure publication in a timely fashion.
7. Establish standards of excellence for DCCT publications.
8. Review, edit, and approve all DCCT publications and presentations prior to submission, enlisting the special assistance of the DCCT committees whenever appropriate. The review will be conducted pursuant to the following editorial policy:
 5. To ensure that all publications preserve the scientific integrity of the DCCT.
 6. To correct factual and conceptual inaccuracies if necessary.
 7. To safeguard the rights of volunteer participants.
 8. To prepare comments to assist collaborating scientists in publishing papers of the highest quality and clarity.
 9. To inform the Steering Committee, NIDDK, and advisory groups of all public dissemination of DCCT information.
 10. To avoid conflict with and/or duplication of other DCCT publications.

7. Review, suggest necessary revisions, and approve any publications arising from approved ancillary studies prior to their submission for publication. In addition to the issues cited in the editorial policy above, proposed publications of ancillary studies will be scrutinized to ensure that their presentation will not threaten the viability of the DCCT, if still ongoing.
8. Suggest appropriate journals for DCCT publications and monitor the process of publication.
9. Perform other writing, reviewing, or editing tasks assigned by the Steering Committee or its Executive Committee.

14.3 Implementation

Procedures for implementation, definition of terms and detailed authorship policies are given in the DCCT Manual of Operations.

15. ANCILLARY STUDIES

15.1 Introduction

Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the DCCT. Ancillary studies which complement the objectives and thereby enhance the value of the DCCT are to be encouraged. Such studies should augment and promote the continued interest of both subjects and investigators. To protect the integrity of the major study, a proposal to conduct an ancillary study must be reviewed and approved by the Ancillary Studies Committee before its initiation. In some cases, ancillary studies must also be approved by the Steering Committee. All approved ancillary studies will be reviewed yearly by the Ancillary Studies Committee for progress and impact on the DCCT as a whole.

15.2 Definition of an Ancillary Study

An ancillary study is defined as research or data collection involving DCCT subjects using any technique, medication, procedure, questionnaire or observation other than those set forth in the DCCT Protocol.

The investigator responsible for the conduct of an ancillary study must be a member of the DCCT Study Group.

15.2.1 Reason for Requirement of Approval

Investigators and subjects are entitled to prior assurance that all ancillary studies are of high scientific merit and that no ancillary study will:

9. Cause a deviation from the Protocol;
10. Complicate interpretation of the study results;
11. Potentially adversely affect subject cooperation;
12. Jeopardize the public image of the study;
13. Create a significant diversion of the study resources locally or at the Coordinating Center or any other DCCT unit;
14. In any way negatively influence the cooperative spirit of the collaborating investigators;
15. Otherwise compromise the scientific integrity of the study.

15.3 Levels of Approval Required for Ancillary Studies

There are two levels of approval for ancillary studies:

Level I: Approval by the Ancillary Studies Committee.

Level II: Further approval by the Steering Committee.

In general, Level I approval will suffice if the ancillary study involves analyzing available data from the DCCT for questions not addressed in the major study, and no additional tests or observations will be made on the subjects. Other types of ancillary research will customarily require both Level I and Level II approval. The decision regarding the necessary level of approval will be made on a case by case basis by the Chairman of the Ancillary Studies Committee in consultation with the Executive and/or Steering Committees.

After approval by the Ancillary Studies Committee and the Steering Committee, final approval is contingent upon the Ancillary Studies Committee receiving a letter signed by the principal and all collaborating investigators in which they agree to abide by the policies for ancillary studies herein described including that regarding publication or presentation of results.

15.4 Funding of Ancillary Studies

The DCCT will not provide funds for ancillary studies. In particular, no funds are provided for Coordinating Center activities or services in support of ancillary studies. If funds are needed, the investigator must explore other avenues such as: (1) submission of a new research grant application; or (2) use of other sources of funds (i.e., a foundation, drug company, etc.). The anticipated source of funds must always be identified.

15.5 Publication of Ancillary Study Results

All manuscripts, abstracts or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the DCCT Publications/Presentations Committee before publication or presentation.

15.6 Implementation

Procedures for the implementation of this policy are given in the DCCT Manual of Operations.

16. PROTOCOL CHANGES

16.1 Introduction

The objectives of Phase III of the DCCT are most likely to be achieved if the Protocol does not require alteration during that phase of the study. Any changes in the Protocol will result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which Protocol changes are necessary.

16.2 Steering Committee Policy

Changes in the Protocol will be recommended by the Steering Committee only if they are required to insure subject safety or will significantly enhance the scientific validity of the study. To recommend Protocol change, .us three-fourths of the Steering Committee must approve the change.

16.3 Procedures

The Planning Committee will consider proposals for Protocol changes which may originate from the DSQ, the NIDDK, the Coordinating Center or one of the working committees. The DSQ will recommend changes on the basis of recruitment information and post-randomization follow-up data. Other groups could propose changes based on procedural or operational factors. The Planning Committee will make a recommendation to the Steering Committee as to whether or not a change of Protocol is warranted and, if so, what form it should take. The recommendations of the Steering Committee will be considered by the DSQ who will advise the NIDDK concerning the proposed change. If the change of Protocol is of sufficient magnitude to represent "a key decision point in the trial" (e.g., a change in fundamental design), the NIDDK will seek the advice of the Policy Advisory Group. NIDDK will make any final decision regarding Protocol change.

17. Organization

17.1 Introduction

The organizational structure of the DCCT has been developed to coordinate the activities of the necessary committees, laboratories, units and review groups, and to assist in the conduct of this trial by ensuring careful and uniform adherence to the Protocol and Manual of Operations.

17.2 Structure

The organizational structure for the DCCT trial is presented in Figure 17.1.

The Director of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) is responsible for the use of Institute funds and the management of Institute programs. He bears ultimate responsibility for the conduct of the DCCT and serves as the final decision-maker for all major issues affecting the DCCT. The Institute Director appoints the Chairmen and members of the Policy Advisory Group (PAG), the Data, Safety and Quality Review Group (DSQ), and the Chairman of the Steering Committee.

The Director, Division of Diabetes, Endocrinology and Metabolic Diseases (DEMD), is the principal representative of the Director of NIDDK and is responsible for ensuring that the scientific and technical goals of the study are consistent with the mission and responsibilities of the NIDDK.

Within the Diabetes Program Branch of the DEMD Division, the Diabetes Clinical Trials Program Office provides liaison between the DCCT Research Group and the NIDDK. This office represents the Institute in all matters which concern the administrative, scientific and technical direction of the trial. A program representative is a member of the study's Executive and Steering Committees and an ex-officio member of each of the working committees. All DCCT communications with the commercial sector (i.e., companies which are vendors of diabetes-related supplies and services) and with the general public are coordinated by the Diabetes Clinical Trials Program Office.

The Policy Advisory Group (PAG), is comprised of individuals who are professional and lay representatives of the diabetes community and not otherwise connected with the trial. The PAG Chairman will serve as an ex-officio member of the DSQ. The PAG will meet every two years and at other times deemed necessary by its Chairman or by the NIDDK Director. They will receive annual reports on the progress of the trial and advise the NIDDK regarding overall trial policy including decisions to make major changes in the Protocol or to conclude the study.

The Data, Safety and Quality Review Group (DSQ) is comprised of individuals not otherwise involved in the trial who are expert in the methodological, operational, medical, psychological, ethical and biostatistical aspects of clinical trials. The DSQ will monitor all study data at regular intervals and has primary responsibility for ensuring patient safety and welfare as well as data quality and analysis. They will review all Protocol changes and ancillary studies and will advise NIDDK regarding substantive Protocol changes, termination of the trial and other major issues that may arise.

The Steering Committee is the representative body of all trial participants. It is comprised of a Chairman, the Principal Investigator from each of the clinical centers, one representative from the NIDDK Clinical Trials Program Office, and one representative from the Coordinating Center. The Chairman is appointed by the Director of NIDDK and the Vice-Chairman is elected by the Steering Committee from among its own members. It provides overall scientific direction for the trial through consideration of recommendations from the working committees. The business of the Steering Committee is conducted in accordance with customary parliamentary procedures. Members unable to attend a meeting may designate an alternate to act on their behalf. Steering Committee recommendations for changes in the Protocol require prior consideration by the appropriate DCCT committee(s) and an affirmative vote by three-fourths of the Steering Committee members (or alternates) present and voting.

The Executive Committee acts in behalf of the Steering Committee during the intervals between Steering Committee meetings to make the day-to-day management decisions needed for the trial to proceed in a smooth, efficient and orderly way. The Executive Committee is comprised of the Chairman of the Steering Committee, the Co-Director of the Coordinating Center, and the Director of the Diabetes Clinical Trials Program Office. Actions taken by the Executive Committee will be reported at the next meeting of the Steering Committee and major decisions (e.g., those that in the opinion of any member of the Executive Committee may affect the integrity of the trial or require a Protocol change) will be made only after consideration by the Steering Committee.

The Planning Committee integrates the activities of the working committees to ensure that material is presented to the Steering Committee in an orderly manner. The makeup of this group includes the Vice-Chairman of the Steering Committee who serves as Planning Committee Chairman, the Chairpersons of the seven working committees, the Director of the Coordinating Center and the three members of the Executive Committee.

The working committees which support the Steering Committee are: Treatment, Standards/Methods, Complications, Eligibility/Adherence, Publications/Presentations, Ancillary Studies and Trial Coordinators. These committees are appointed by the Steering Committee Chairman from among the professional personnel from each of the clinical centers, the Coordinating Center staff, the NIDDK staff, and necessary consultants. The three members of the Executive Committee are ex-officio members of each of the working committees.

More description is provided below regarding the nature of the activities of the clinical centers, the working committees, the Clinic Monitoring Group, the Coordinating Center, and the central study units.

1. Clinical Centers. The clinical centers are staffed by a Trial Coordinator and other necessary personnel under the supervision of a Principal Investigator. The Principal Investigator will work with the Coordinating Center, Chairman of the Steering Committee, and NIDDK staff assigned to this project to conduct the study in accordance with the Protocol and Manual of Operations. The clinical centers are expected to meet the patient recruitment goals as specified by the Coordinating Center and will work with the Central Ophthalmologic Reading Unit, the Central Biochemistry Laboratory, the Coordinating Center, and other central units to maintain the quality of the data.
2. Working Committees. All working committees have specific responsibilities as outlined below and will assume such other responsibilities as requested by the Steering or Executive Committee(s).

- a) Treatment. The Treatment Committee will consider any and all proposals to update and revise the treatment strategies described in the Protocol and Manual of Operations and make recommendations to the Steering Committee via the Planning Committee. The Treatment Committee will review modification of the treatment regimen. Periodically, they will review deviation from treatment and transfer to inactive status. All products and/or devices used by the clinical centers to implement the treatment strategies must have the prior approval of the Treatment Committee. They will also revise, update and develop additional guidelines for the management of intercurrent events. The Treatment Committee will provide consultation to the clinical centers regarding implementation of the treatment protocol.
- b) Standards/Methods. The Standards/Methods Committee will assist the Coordinating Center in monitoring the performance of the Central Biochemistry Laboratory and the Central Nutrition Coding Unit. They will consider any and all proposals for changes in the procedures used for making the measurements performed by these laboratories/units as specified in the Protocol and Manual of Operations. They will consider the need for additional laboratory procedures and/or the deletion of ongoing laboratory procedures and make recommendations to the Steering Committee via the Planning Committee.
- c) Complications. The Complications Committee is responsible for review and consideration for presentation to the Planning and Steering Committees of all matters pertaining to primary prevention and secondary intervention study endpoints. They will assist the Coordinating Center in monitoring the performance of the Central Ophthalmologic Reading Unit, the Central EKG Reading Unit, the Central Neurobehavioral Coding Unit and the Central Autonomic Coding Unit. They will consider any and all proposals for changes in the procedures used for making the measurements performed by these laboratories/units as specified in the Protocol and Manual of Operations. They will consider the need for additional reading or coding unit procedures and/or the deletion of ongoing reading or coding unit procedures and make recommendations to the Steering Committee via the Planning Committee.
- d) Eligibility/Adherence. The Eligibility/Adherence Committee will assist the Coordinating Center in interpreting the eligibility/exclusion criteria specified in the Protocol and Manual of Operations. They will consider any and all proposals for changes in these criteria and make recommendations to the Steering Committee via the Planning Committee. They will assist the Coordinating Center in monitoring patient adherence, in promoting the implementation of ongoing adherence programs, and in developing additional strategies intended to optimize patient adherence.
- e) Publications/Presentations. The Publications/Presentations Committee will implement the policies and procedures pertaining to all DCCT publications, presentations, media releases, interviews, and other communications as specified in Section 14 and in the Manual of Operations.

- f) Ancillary Studies. The Ancillary Studies Committee will implement the policies and procedures pertaining to all DCCT ancillary studies as specified in Section 15 and in the Manual of Operations.
 - g) Trial Coordinators. The Trial Coordinators Committee will review and consider the impact of proposed ancillary studies and changes in the Protocol and Manual of Operations on the day-to-day activities of the clinical centers and on patient adherence. They will make recommendations to the Steering Committee via the Planning Committee. They will assist the Coordinating Center in evaluating proposed changes in the data forms and in updating the Trial Coordinators Handbook. They will also assist the Coordinating Center in ensuring that DCCT personnel are adequately trained and certified so that study data are collected and reported in a standardized way and that the Protocol and Manual of Operations are implemented in a uniform manner.
3. Clinic Monitoring Group. The Clinic Monitoring Group (CMG) is appointed by the Steering Committee Chairman to assist the Steering Committee and especially its Executive Committee in monitoring the performance of the clinical centers as specified in Section 10.3. The CMG is comprised of four physician investigators, one of whom is appointed as Chairman, and one Trial Coordinator. The three members of the Executive Committee serve as ex-officio members. The Coordinating Center provides the CMG with the operational study data (as opposed to masked, outcome study data) that will enable them to monitor clinic adherence to the Protocol and Manual of Operations in a timely fashion.
4. Coordinating Center. The Coordinating Center will participate in all aspects of the design and implementation of the DCCT. The Director of the Coordinating Center or his designee is a member of the Planning Committee and the Steering Committee and the Co-Director is a member of the three-person Executive Committee. Coordinating Center personnel will provide scientific, technical and staff services to the Steering Committee and each of its working committees/groups. The Coordinating Center has the responsibility for implementing the systems necessary for data collection, editing, management and statistical analysis and for the maintenance of permanent study records and files. They have the responsibility of providing appropriate and timely data reports to the Executive Committee, the CMG, the DSQ and its subcommittees, the PAG, and to the NIDDK Director. They are responsible for all aspects of intrastudy communication and will work with the Publications/Presentations Committee in providing appropriate statistical analyses of study data in a timely fashion for use in approved publications and presentations. The Coordinating Center will implement its responsibilities as specified in its internal procedures manual, ensuring that study data are safely maintained and not released in an unauthorized manner. The following seven central units are the responsibility of the Coordinating Center. In general, these units provide scientific and technical guidance to the Study Group, specific working committees and the Coordinating Center.
- a) Central Ophthalmologic Reading Unit. The Central Ophthalmologic Reading Unit will receive and evaluate the quality of all photographs of the eye; utilize the modified ETDRS classification system for evaluating the grading of fundus photographs, as described in Sections 4, 6.3 and 9.3, and maintain study records of all photographic data.

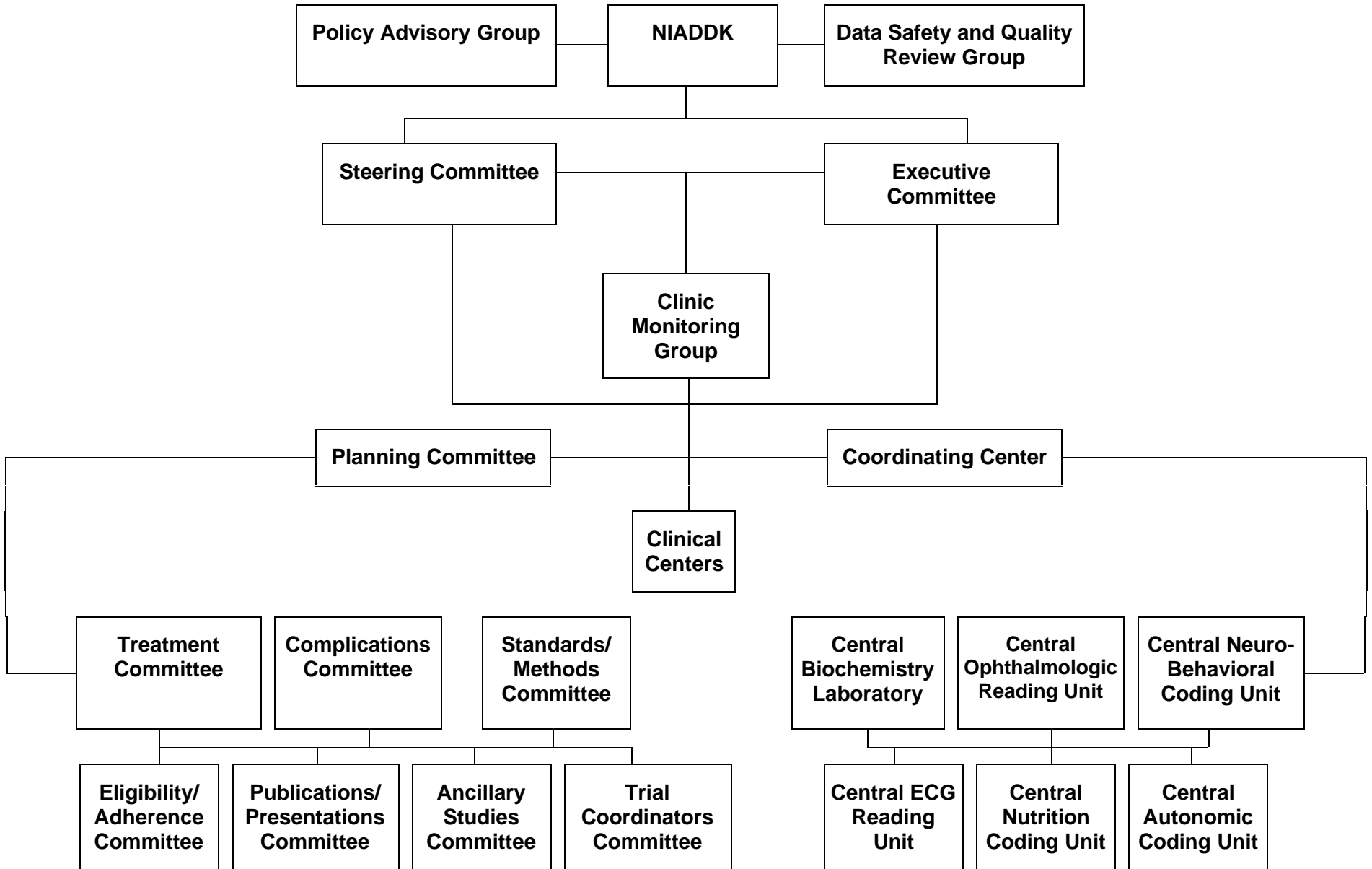
- b) Central Biochemistry Laboratory. The laboratory will provide eligibility baseline and repeated measurements of HbA1c, blood glucose, lipids, and other serum and urine constituents as described in Sections 6.2, 6.4, 9.2 and 9.4.
- c) Central EKG Reading Unit. The Central EKG Reading Unit will provide baseline and follow-up coding of all EKG tracings from eligible patients as described in Sections 6.5 and 9.5.
- d) Central Nutrition Coding Unit. The Central Nutrition Coding Unit will provide baseline and follow-up analysis and coding of diet history data as described in Sections 6.9 and 9.9.
- e) Central Neurobehavioral Coding Unit. The Central Neurobehavioral Coding Unit will provide scoring and coding of baseline and follow-up analysis of performance results of the neurobehavioral test battery as described in Sections 6.6 and 9.6.
- f) Central Autonomic Coding Unit. The Central Autonomic Coding Unit will provide baseline and repeated coding of the results of tests of autonomic nervous system function as described in Sections 6.5 and 9.5.

17.3 Morbidity/Mortality Classification Committee

The Morbidity/Mortality Classification Committee is a wholly independent committee established by NIDDK to review and classify all deaths and major intercurrent events that occur among patients randomized into the DCCT. The events reviewed and classified will include: death, major accident, myocardial infarction, cerebrovascular accident with persistent neurological deficit, non-traumatic amputation, loss of vision, renal insufficiency, and neuropathy, as defined in the Manual of Operations. The purpose served by these reviews will be to: determine the primary and contributing causes of death, validate the basis for diagnosis of morbid events, and determine the likelihood that the event is attributable to diabetes. The classifications by this committee will be the basis of statistical analyses for the DCCT.

Figure 17.1

Organizational Structure for Phase III



18. DISPOSITION OF DOCUMENTS, DATA, AND MATERIALS

18.1 Documents

During the course of the DCCT, all principal documents (Protocol, forms and manuals) will be available from the Coordinating Center upon the request of any member of the DCCT Research Group. At the conclusion of the DCCT, these documents will be archived at the Coordinating Center and deposited with the National Technical Information Service (NTIS). Minutes of the meetings of the major Committees and Groups will be kept on file at the Coordinating Center. At the termination of the DCCT, the microfilm of the minutes of all the meetings of the Planning Committee, the Steering Committee, the PAG and the DSQ will be transferred to the NIDDK.

18.2 Data Forms

The Coordinating Centers copies of the subject data forms will be microfilmed (microfiched) and retained at the Coordinating Center. A copy of the microfiche file will be made available to the NIDDK. This file will not contain any subject identifiers. The subject data files within each clinical center will be retained as a part of the medical record of that institution to which state law or hospital requirements for the disposition of medical records apply.

18.3 Tapes of Data and Analysis Files

At the conclusion of the DCCT, a standard computer tape containing all DCCT data will be deposited with the National Technical Information Service (U. S. Department of Commerce, Springfield, Virginia) with documentation of its contents. This data tape will then be available to the general public and other scientific investigators at a nominal charge.

For each of the principal study manuscripts, the Coordinating Center will also prepare an analysis tape containing the data used for the analyses of that manuscript and that tape will also be deposited with the National Technical Information Service with appropriate documentation. The Coordinating Center will also prepare a detailed description of all statistical analyses conducted to support statements made in each principal manuscript and this document will also be filed with the National Technical Information Service.

18.4 Laboratory Specimens

Laboratory specimens received by the Central Biochemistry Laboratory will be maintained in long-term storage until the conclusion of the DCCT. At that time, an announcement will be published offering these specimens to interested investigators. Specimens not claimed will then be destroyed.

18.5 Photographs and Other Materials

Photographic materials received by the CORU will also be stored until the conclusion of the DCCT. At that time, the Steering Committee will evaluate the future scientific value of these materials. If it is determined that the photographs will not be of value to other investigators, they

will then be offered to each clinical center as a part of each subjects medical record. The materials not claimed by individual subjects or their clinical centers will then be destroyed.

18.6 Policy of External Distribution of Documents During the Conduct of the Study

The NIDDK will maintain a list of study documents and publications that will be available upon request.

Appendix A

DCCT Form 031.3
March 3, 1986

INFORMED CONSENT FORM #1 (PROTOTYPE)

Diabetes Control and Complications Trial (DCCT)

Institution: _____

Principal Investigator: _____

1. I have been told that I may be eligible for participation in the Diabetes Control and Complications Trial (DCCT).
2. I have been given copies of the DCCT Research Volunteers Information Handbook and the Manual of Diabetes Tests, Terms and Special Procedures. I have read both of these, I have had my questions answered, and I now clearly understand the following:
 - a) The purpose of the study. (Research Volunteers Information Handbook, pages 4-6)
 - b) The nature of a clinical trial. (Research Volunteers Information Handbook, page 5)
 - c) The two groups to be studied -- the Standard Group and the Experimental Group -- and the fact that there is no proven advantage to being placed in one group or the other. (Research Volunteers Information Handbook, pages 5 and 8)
 - d) The fact that I shall be assigned to one of these two groups based on a process called random assignment, which means that neither my doctor nor I can choose to which group I will be assigned. Instead, I will be assigned by chance. I am willing to accept an assignment to either of the two treatment groups. (Research Volunteers Information Handbook, page 5)
 - e) That blood tests and urine tests (including tests I will perform at home) will be used to measure diabetes control. (Research Volunteers Information Handbook, pages 8-9; Manual of Diabetes Tests, Terms and Special Procedures, page 12)
 - f) That special tests of my eyes, kidneys, nervous system, heart, blood vessels, and psychological tests will be conducted to look for the appearance or progress of early diabetes complications. (Research Volunteers Information Handbook, page 10; Manual of Diabetes Tests, Terms and Special Procedures, pages 4-8)

I have been given a complete description of these special tests in the Manual of Diabetes Tests, Terms and Special Procedures. I understand that if I am eligible to volunteer for this clinical trial, I shall be given a thorough explanation in writing of any tests not covered below before I am asked to sign a second permission form for those tests.

- g) The responsibilities I agree to carry out if I decide to be a volunteer for the clinical trial involve my willingness to follow the treatment program of the group to which I have been assigned and to keep my appointments as scheduled. I understand that some of these appointments will take considerable time. (Research Volunteers Information Handbook, pages 12-13)

I also understand that my responsibilities will include blood tests and urine tests I will do at my home. One of the required blood tests is a 3:00 a.m. sample. I will also keep records of my test results and treatment program, even though this may be time consuming. (Research Volunteers Information Handbook, pages 8-9; Manual of Diabetes Tests, Terms and Special Procedures, page 12)

3. I have had a chance at this time to ask all questions which I feel are necessary. I now feel I have enough understanding to allow me to make a preliminary decision about my participation in this clinical trial.
4. Understanding the above, and having been made aware of the potential risks and benefits of the overall program (Research Volunteers Information Handbook, pages 14-15; Manual of Diabetes Tests, Terms and Special Procedures, pages 4-12), I give you my permission to conduct the tests and procedures necessary to see whether I will qualify as a volunteer for the DCCT. I do this because I am willing to consider volunteering for participation in the DCCT if I do qualify.

I understand that if any of the test results show that I am not eligible to be in the trial, the rest of the tests will not be done. If this happens, I will be informed of the reasons why I will not be eligible to participate in the trial. I understand some test results may make me ineligible, even though they have nothing to do with the state of my health.

5. I specifically give my permission at this time for the following:
- a) A complete medical history and physical examination. I understand that there is no risk involved in this thorough examination, and that there may be some benefit to me in terms of my being more aware of my exact health.
 - b) Collection of urine samples at different times; these samples will be used for various tests. There is no risk involved in this procedure. One test involves four hour timed urine collection during a visit to the center.
 - c) The collection of approximately two ounces of my blood from a vein in my arm, a procedure which will be carried out by a skilled technician. This blood sample will be used for various laboratory tests. I understand that there is a very small risk of a black and blue mark when this procedure is done. One blood sample will be taken after I drink four ounces of a commonly used formula which is not pleasant tasting. This drink may make me sick to my stomach. (For women: I understand that one of the tests which will be performed on a blood or urine sample will tell me whether or not I am pregnant.)
 - d) A thorough eye examination by an eye specialist using standard techniques. This will include a test of my vision and a measurement of the pressure in my eyes. To carry out these tests, drops will be put in my eyes to make them dilate; I understand some people

find this uncomfortable. I know that I will not be able to drive, or read clearly, for a few hours after this test.

Photographs will be taken of my eyes. If I have had diabetes for less than five years, additional photographs of my eyes may be taken after a dye called fluorescein has been injected into a vein in my arm. I understand that both these techniques are used in standard clinical practice, but there may be some discomfort associated with each. With fluorescein I understand that it is also possible that I shall experience some nausea. I have also been told that on rare occasions some people have a very serious allergic reaction to this dye. I understand that trained personnel will be available when I take the test to lessen the possibility of any such reaction, or to treat it should it occur.

- e) I agree to undergo evaluation of my nervous system. This evaluation will consist of a thorough physical examination in which my strength, reflexes and sensations will be tested. Then I will undergo a nervous system evaluation (nerve conduction test) to evaluate certain nerve functions. Some people feel a slight pain during this test. In other people, the test produces a temporary numb feeling. I agree to undergo a test of my autonomic nervous system by means of a special tape recording electrocardiogram.
- f) I understand that a standard electrocardiogram will be done. There is no risk or discomfort involved in this test.
- g) I agree to take several psychological tests. I recognize that this testing is being performed to determine if it is in my best interest to be included in the trial. The tests are designed to be sure I have no problems that could interfere with my participation in the trial. The tests will include:

- 1) Questionnaires: Several paper and pencil tests will be given to me to complete.
- 2) A formal interview with a member of the health care team.

I agree to participate in other meetings, which will include my family or a person I live with, in which the various procedures involved in this clinical trial will be discussed.

A few people find some of the questions embarrassing. I understand that I may refuse to answer such a question.

I understand that all information obtained during these interviews will be confidential. The results will be given to my doctor only if the results will have an effect on my participation in the study. No information will be released to anyone else without my specific consent.

- 6. I also agree to carry out to the best of my abilities several tasks, some at home, as part of this program to see if I qualify to be a participant in the DCCT. These include:
 - a) Keeping records about my current treatment program for two weeks.
 - b) Meeting with members of the health care team to review my program.
 - c) Collecting blood samples at home. (Two 3:00 a.m. self blood glucose monitoring samples will be required during this two-week period.)

7. I understand that I will be given a questionnaire to test my understanding of the objectives and nature of the DCCT. I understand that I must answer 100% of these questions correctly before I will be considered qualified to be a participant in the DCCT. If I give the wrong answer to any of the questions, I understand that I must come back another day to retake the questionnaire. If I feel that I would benefit from viewing the orientation slide show or by re-reading the Research Volunteers Handbook, I may do so. If I have any questions regarding my incorrect answers, I would be able to discuss them with a member of the team before taking the questionnaire again. If I do not answer correctly all the questions on the second test, I understand the DCCT physician will decide whether I understand the objectives and nature of the DCCT.
8. I understand that during the period of this study (if I am accepted as a volunteer), my doctor at the center will be made aware of all information that may affect my personal care. However, I also understand that my doctor may not be aware of possible beneficial or detrimental results from my involvement in the study, until it is determined by an independent group of experts that these data are conclusive and meaningful. The results of some tests may not be made known to my physician or to me unless a change in my treatment is needed. (Research Volunteers Information Handbook, pages 5 and 11)
9. I understand that the choice I have is to volunteer to participate in the DCCT and have the DCCT health care team take care of me or to continue in my present program for diabetes management with my current doctor.
10. I understand that I may choose not to participate in the DCCT, or that I may change my mind at any time concerning participation, without placing in jeopardy my continuing medical care.
11. I understand that the information concerning my diabetes will be combined with that of many other volunteers, and that I will not be personally identified in any publications or public documents which result from this study.
12. Neither this institution nor the government agency funding this research project will automatically provide special services, free care, or compensation for any injuries or adverse reactions resulting from this research. Treatment for such injuries or adverse reactions will be provided under the same financial arrangement as those under which treatment is usually provided.

If I believe that I may have suffered any injury or adverse reaction as a result of participating in this research, or have questions about my rights as a research subject, I may contact Dr. _____ (_____) or the Associate Vice President of this medical center (_____). They can review the matter with me, identify other resources that may be available to me, and provide me with further information as to how to proceed.

Signature _____

Date _____

Witness _____

(IN THE CASE OF A VOLUNTEER UNDER 18 YEARS OF AGE)

We, as parents or legal guardians of _____, have read and understand this material, have had our questions answered, and give our permission for our child to participate in this clinical trial. (Both parents should sign, if available.)

Signature _____

Date _____

Witness _____

Signature of Principal Investigator _____

Date _____

Witness _____

Appendix B

DCCT Form 032.3
March 3, 1986

INFORMED CONSENT FORM #2 (PROTOTYPE)

Diabetes Control and Complications Trial (DCCT)

Institution: _____

Principal Investigator: _____

1. I have been told that I am eligible to participate in the Diabetes Control and Complications Trial (DCCT).

2. I have been given copies of the DCCT Research Volunteers Information Handbook and the Manual of Diabetes Tests, Terms and Special Procedures. I have read both of these, I have had my questions answered, and I now clearly understand the following:
 - a) The purpose of the study. (Research Volunteers Information Handbook, pages 4-6)
 - b) The nature of a clinical trial. (Research Volunteers Information Handbook, page 5)
 - c) The two groups to be studied -- the Standard Group and the Experimental Group -- and the fact that there is no proven advantage to being placed in one group or the other. (Research Volunteers Information Handbook, pages 5 and 8)
 - d) The possible risks and benefits of being assigned to the Standard Group or the Experimental Group. (Research Volunteers Information Handbook, pages 14-15; Manual of Diabetes Tests, Terms and Special Procedures, pages 4-12)
 - e) The fact that I shall be assigned to one of these two groups based on a process called random assignment, which means that neither my doctor nor I can choose to which group I will be assigned. Instead, I will be assigned by chance. I am willing to accept an assignment to either of the two treatment groups. (Research Volunteers Information Handbook, page 5)
 - f) That blood tests and urine tests (including tests I will perform at home) will be used to measure diabetes control. (Research Volunteers Information Handbook, pages 8-9; Manual of Diabetes Tests, Terms and Special Procedures, page 12)
 - g) That special tests of my eyes, kidneys, nervous system, heart, blood vessels, and psychological tests will be conducted during the trial to look for the appearance or progress of early diabetes complications. I have been given a complete description of

these special tests in the Manual of Diabetes Tests, Terms and Special Procedures. (Research Volunteers Information Handbook, page 10; Manual of Diabetes, Tests, Terms and Special Procedures, pages 4-8)

- h) I understand the extent of the responsibilities I agree to carry out if I agree to be a volunteer for the clinical trial. These involve my willingness to follow the treatment program of the group to which I have been assigned and to keep my appointments as scheduled. I understand that some of these appointments will take considerable time. (Research Volunteers Information Handbook, pages 12-13)

I also understand that my responsibilities will include blood tests and urine tests I will do at my home. One of the required blood tests may be a 3:00 a.m. sample once a week. I will also keep records of my test results and treatment program, even though this may be time consuming.

- i) I am agreeing to participate in a clinical trial that may last for .us seven years. I understand that the study could end early if the study questions have been answered or for reasons of safety. (Research Volunteers Information Handbook, pages 12-13)

3. I have had a chance at this time to ask all questions which I feel are necessary. I now feel I have enough understanding to allow me to decide to participate in this clinical trial.

4. Understanding the above, and having been made aware of the potential risks and benefits of the overall program, I give you my permission to conduct the tests and procedures listed below during the clinical trial. I further understand that if any new tests are required, I shall be given a thorough explanation in writing before I am asked to sign another permission form covering these new tests.

5. I specifically give my permission at this time for the following tests and examinations:

- a) A complete medical history and physical examination. I understand that there is no risk involved in this thorough examination, and that there may be some benefit to me in terms of my being more aware of my exact health. This examination will be done once a year.
- b) Collection of urine samples once a year; these samples will be used for various tests. There is no risk involved in this procedure. One test involves a four hour timed urine collection during a visit to the Center once a year. Another test requires a 24 hour collection of urine at home.
- c) The collection of blood from a vein in my arm, a procedure which will be carried out by a skilled technician. These blood samples will be used for various laboratory tests. I understand that there is a very small risk of a black and blue mark when this procedure is done. These blood tests which will require about one tablespoon of blood will be done routinely at three-month intervals in the Standard Treatment Group and monthly in the Experimental Treatment Group. At the annual clinic visit, an additional two tablespoons of blood will be taken.
- d) A complete and thorough eye examination by an eye specialist using standard techniques. This will include a test of my vision every year and a measurement of the pressure in my eyes every year. To carry out these tests, drops will be put in my eyes to

make them dilate; I understand some people find this uncomfortable. I know that I will not be able to drive, or read clearly, for a few hours after this test.

Photographs will be taken of my eyes at six-month intervals. If I have had diabetes for less than five years, a set of additional photographs of my eyes may be taken in five years and at the conclusion of the study and for this a dye called fluorescein will be injected into a vein in my arm. I understand that both these techniques are used in standard clinical practice, but there may be some discomfort associated with each. With fluorescein I understand that it is also possible that I shall experience some nausea. I have also been told that on rare occasions some people have a very serious allergic reaction to this dye. I understand that trained personnel will be available when I take the test to lessen the possibility of any such reaction, or to treat it should it occur.

- e) I agree to undergo evaluation of my nervous system in five years and at the conclusion of the study. This evaluation will consist of a thorough physical examination in which my strength, reflexes and sensations will be tested. Then I will undergo a peripheral nervous system evaluation (nerve conduction test) to evaluate certain nerve functions. Some people feel a slight pain during this test. In other people, the test produces a temporary numb feeling. Every two years, I agree to undergo a test of my autonomic nervous system.
- f) I understand that a standard electrocardiogram will be done. There is no risk or discomfort involved in this test. The electrocardiogram will be done every two years.
- g) I agree to take several psychological tests. The tests will include:
 - 1) Questionnaires: Several paper and pencil tests will be given to me to complete every year.
 - 2) A series of tests (neurobehavioral assessment) of my intelligence, memory, problem-solving ability, motor coordination and attention will be performed at the beginning of the trial and every year thereafter.

A few people find some of these questions embarrassing. I understand that I may refuse to answer such questions.

I understand that all information obtained during these interviews and tests will be confidential. The results will be given to my doctor only if the results will have an effect on my personal care. No information will be released to anyone else without my specific consent.

- h) The investigators of this trial are asking me to participate in a new and more accurate means of measuring my kidney function that has become available. This is called the 125-I Iothalamate Glomerular Filtration Rate Determination. This test involves a subcutaneous injection (given just like insulin) of a compound that contains a small amount of radioactive iodine. This substance is absorbed and will be measured in my blood and urine (five times) over a period of several hours. This study will be done as part of the baseline examination, the three-year annual examination and at the end of the study.

125-I Iothalamate has been approved for intravenous injection in humans by the Food and Drug Administration (FDA). Subcutaneous injection has been approved for investigative purposes by the FDA. However, subcutaneous injection has been extensively used in many centers in the United States. The administered dose contains less than 35 microcuries. The total amount of radiation is less than 1/100 of a chest x-ray. The compound 125-I Iothalamate is efficiently excreted by the kidneys and is not stored in the body. At the end of 24 hours, less than 1/10,000 of a dose will remain in the body. The risks involved are those of having blood drawn and possible allergic reactions to the iodine or Iothalamate. I will be given a few drops of inorganic iodine prior to the test to block any uptake by the thyroid. If I am a woman, I should not be pregnant at the time of the test and will have a serum pregnancy test performed within 72 hours prior to the test. I understand that the choice I have is to volunteer for this part of the DCCT or refuse this test. I can still participate in the DCCT even if I do not agree to have this test performed.

6. I understand that if I am a woman, I am not planning to become pregnant in the next 2 years.
7. I understand that during the period of this study my doctor at the center will be made aware of all information that may affect my personal care. However, I also understand that my doctor may not be aware of possible beneficial or detrimental results from my involvement in the study until it is determined by an independent group of experts that these data are conclusive and meaningful. The results of some tests may not be made known to my physician or to me unless a change in my treatment is needed. (Research Volunteers Information Handbook, pages 5 and 11)
8. I understand that the choice I have is to volunteer to participate in the DCCT and have the DCCT health care team take care of me or to continue in my present program for diabetes management with my current doctor.
9. I understand that I may choose not to participate in the DCCT, or that I may change my mind at any time concerning participation, without in any way placing in jeopardy my continuing medical care or incurring any danger or health risk provided I continue on an appropriate insulin regimen.
10. I understand that the information concerning my diabetes will be combined with that of many other volunteers, and that I will not be personally identified in any publications or public documents which result from this study.
11. Neither this institution nor the government agency funding this research project will automatically provide special services, free care, or compensation for any injuries or adverse reactions resulting from this research. Treatment for such injuries or adverse reactions will be provided under the same financial arrangement as those under which treatment is usually provided.

If I believe that I may have suffered any injury or adverse reaction as a result of participating in this research, or have questions about my rights as a research subject, I may contact Dr. _____ (_____) or the Associate Vice President of this medical center (_____). They can review the matter with me, identify other resources that may be available to me, and provide me with further information as to how to proceed.

Signature_____

Date_____

Witness_____

My signature below also signifies my willingness to participate in the 125-I lothalamate study.

Signature_____

Date_____

Witness_____

(IN THE CASE OF A VOLUNTEER UNDER 18 YEARS OF AGE)

We, as parents or legal guardians of _____, have read and understand this material, have had our questions answered, and give our permission for our child to participate in this clinical trial. (Both parents should sign, if available.)

Signature _____

Date _____

Witness _____

Signature of Principal Investigator _____

Date _____

Witness _____