Epidemiology of Diabetes Interventions and Complications Study (EDIC)

Protocol: 2017-2022

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1. BACKGROUND

The long-term microvascular, neurologic, and macrovascular complications of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) cause major morbidity and mortality (1). Despite major advances in the treatment of diabetic retinopathy with photocoagulation (2,3), vitrectomy and anti-VEGF injections (4), it remains the major cause of new onset blindness in adults in the U.S (1). Diabetic nephropathy is the most common cause of end-stage renal disease in adults (1,5). Diabetes increases the risk of non-traumatic amputation by more than forty-fold compared with the non-diabetic population and accounts for more amputations in the U.S. than any other cause (1). Finally, the major cause of mortality in diabetes is cardiovascular disease. Diabetes is associated with a two to seven-fold increase in cardiac and cerebral vascular disease (6-8). The estimated cost of these complications in the aggregate was in excess of $20 billion per year in 1987 (9) and by 2012, total costs associated with diabetes and its complications were $245 billion (10).

Despite the recognized cost in human suffering, loss of productivity, and expense associated with medical care and disability attributable to these complications, there continue to be limited data on the occurrence, pathogenesis, associated risk factors, interactions and co-occurrence of advanced microvascular and macrovascular complications in T1DM. The Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, have established the short-term and longer-term impact of intensive diabetes therapy on retinopathy, nephropathy, neuropathy, and cardiovascular disease (CVD) (11,12). In addition, the DCCT/EDIC has defined the roles of hyperglycemia and other risk factors on the development and progression of complications. The previous results of DCCT/EDIC have been seminal in developing the modern-day therapy of T1DM that has been adopted worldwide (12). Improvements in screening for T1DM-related complications, monitoring, metabolic treatment and management of other risk factors, and treatment of outcomes, have resulted in individuals with T1DM living longer. Thus, there is now the unique opportunity to study the impact of aging on complication progression as well as the impact of diabetes on the aging process.

The Diabetes Control and Complications Trial (**DCCT, 1982-1993**) and the Epidemiology of Diabetes Interventions and Complications (**EDIC, 1994-present**) follow-up study have been ongoing for 33 years (**Figure 1**). The DCCT was a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy, as practiced in 1982, with regard to their effects on the development and progression of the early vascular and neurologic complications of insulin-dependent diabetes mellitus (11). The DCCT defined the role of glucose control in the development and progression of the long-term complications of diabetes. Longitudinal follow-up of the DCCT cohort continued in the EDIC study (12-14), with the goal of examining the longer-term effects of the original DCCT interventions, based on an intention-to-treat analysis, particularly as they applied to longer-term complications, especially advanced stages of microvascular complications, cardiovascular disease, and mortality. During the transition from DCCT to EDIC, the original conventional treatment group was taught intensive therapy and all participants were returned to their own health care providers for diabetes care.

The DCCT/EDIC cohort has been followed with consistent, validated methods since participants entered the study in 1983-1989. In concert, the DCCT and EDIC follow-up have provided more information than any other study of T1DM regarding the relationship among glycemia (15,16) and other risk factors with long-term complications (17), the complications of intensive therapy (18,19) and the effects of glycemic therapy (11,12). With a mean total follow-up of approximately 29 years, 94% of the surviving original cohort actively participating in the study, and more than 275 publications (20), the DCCT/EDIC cohort represents the most carefully studied group of subjects with T1DM in history.

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Figure 1. Timeline of DCCT/EDIC
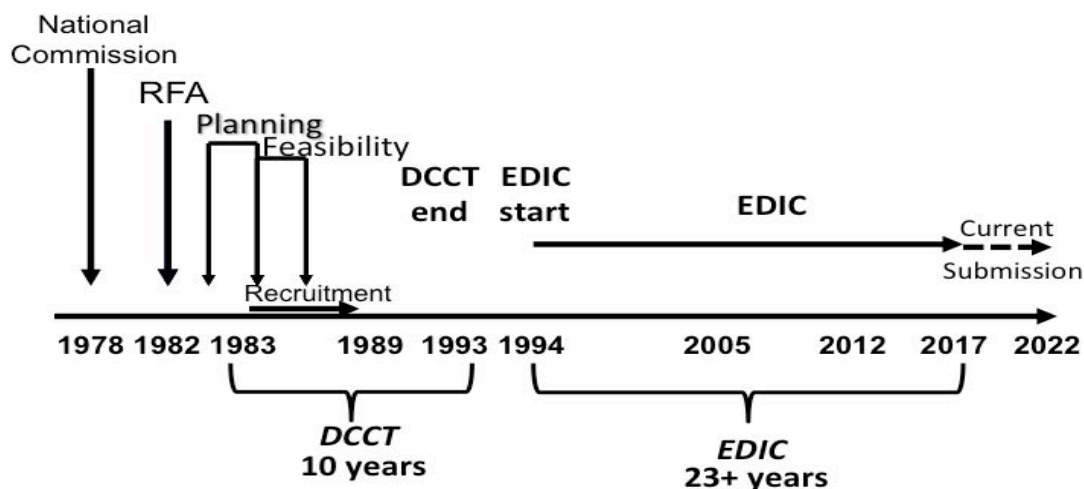
1.1   EDIC years 1-18, 1994-2012

During the first 18 years of EDIC (**EDIC years 1-18, 1994-2012**), the Research Group established the importance of chronic glycemia, among other risk factors, on microvascular and cardiovascular complications; the persistent beneficial effects of the original intensive therapy compared with conventional therapy despite the equalization of chronic glycemia exposure during EDIC, so-called "metabolic memory"; the beneficial effects of intensive therapy on markers of atherosclerosis, including carotid intima-media thickness and coronary artery calcification, and on cardiovascular events; and the extent of microvascular and cardiovascular complications and their long-term effects on quality-of-life and health care costs over time (12, 21-26).

1.2   EDIC years 19-24, 2012-2017

During the most recent five years of funding (**EDIC years 19-24, 2012-17**), EDIC performed further follow-up of the DCCT/EDIC cohort with the goals of: determining the very long-term effects of the original DCCT interventions on *advanced* complications; exploring the longevity of the "metabolic memory" phenomenon; delineating the modern-day clinical course of diabetic complications including the interactions among complications and co-occurrence of complications; examining the long(er) term effects of intensive vs. conventional therapy on cardiovascular events and mortality; exploring the pathophysiologic mechanisms that underlie the development and progression of microvascular, neurologic, and cardiovascular complications; and defining the very-long-term quality of life and economic impacts of intensive therapy.

The statistical approach to analyzing the effects of the original DCCT interventions on relatively rare events, such as mortality, relies on an event-driven or maximum information policy whereby analyses are only conducted after adequate statistical information has been accrued, pre-specified to be a minimum of 50 cases in the conventional treatment group. Similarly, EDIC policy has been to conduct risk factor analyses only after 100 cases in the conventional group have been observed. Both policies provide adequate power to assess specific objectives. The details are described in the Statistical Analysis Plan.

During the most recent funding period (**2012-2017**), the DCCT/EDIC Research Group has published an average of >20 papers per year and has completed, or is in the process of

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completing, all of the major aims proposed in our 2012 grant submission with the following results:

1. Metabolic memory appears to last for approximately 15 years after the end of the DCCT and then wanes (27,28),
2. The early benefits of intensive therapy on microvascular complications translate over time into substantial benefits for *advanced* complications including a significant reduction in the development of renal impairment (29), the development of severe retinopathy requiring laser therapy and surgery (30) and reduced lower extremity ulcers and amputations (31).
3. The originally demonstrated salutary effect of intensive therapy on cardiovascular disease in 2005 (32) has persisted with some attenuation (33).
4. With a greater number of CVD events accruing over time, major CVD risk factors have been defined (34).
5. The original Intensive therapy group has benefited with a 33% reduction in mortality (35); moreover, the standardized mortality rate is now similar to that of the general population (36).
6. The prevalence and risk factors for musculoskeletal complications (cheiropathy) have been defined (37).
7. The DCCT/EDIC Research Group has published a rational frequency for retinopathy screening based on its empiric data (38).
8. The analyses of the impact of T1DM and its complications on quality-of-life and the economic consequences of T1DM and its treatment have been updated (submitted).

In addition to these major aims, DCCT/EDIC has continued to explore, often as a contributing member to genetics consortia, the genetic factors that influence diabetes complications including albuminuria, glycation, various ophthalmologic conditions, and cardiac disease (39-42). We have also completed, or initiated, a series of sub-studies and ancillary studies, funded independently but performed by the Research Group (**Figure 2**).

These ancillary studies are exploring hearing loss as a putative complication of type 1 diabetes, the prevalence and clinical implications of preserved C-peptide secretion in very long-term type 1 diabetes in the EDIC cohort, the relationship between glycemia, and especially hypoglycemia measured using continuous glucose monitoring technology on cardiac rhythm, the prevalence and risk factors for gastroparesis (43), and the urologic complications of type 1 diabetes (44-49).

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Figure 2. EDIC Ancillary Studies, Sub-studies and Collaborations

NIH Grants
- 1992: DCCT Family Study
- 1993: Lipoproteins
- 1993: Mechanisms Vascular Disease
- 1998: Central Obesity
- 2001: Genetic Family
- 2003, 2010: UroEDIC I and II
- 2004: Neurocognitive
- 2008: Biomarkers Vascular Disease
- 2009: CVD Biomarkers
- 2010: Vitamin D
- 2013: Oxidative Biomarkers
- 2013: Hearing Impairment
- 2013: ReproEDIC
- 2015: Expanded Epigenetics
- 2015: C-peptide
- 2016: Hypo-Arrhythmia
- 2016: Leukocyte Endothelial Adhesion
- 2017: Neuroimaging

DCCT/EDIC Core

Other Funding
- 2009: Skin Autoflourescence
- 2011: Epigenetics
- 2013: Gastric Emptying
- 2013: Dermal AGEs

Core Supplements
- 1994, 1998, 2004: Carotid Ultrasound
- 2000: Coronary Calcium
- 2006, 2009: Neurology
- 2007: Cardiac MRI
- 2007: Fundus Comparison Methods
- 2011: C-peptide Pilot
- 2016: Skeletal Health

2012-2017 Core New Initiatives
- Cheiroarthropathy
- Haptoglobin
- Glycated Albumin

1.3   EDIC years 24-28, 2017-2022

The demonstration of very long-term benefits of the original DCCT intensive therapy intervention, including benefits on mortality (36,37), and the extraordinary loyalty of the DCCT/EDIC cohort, have provided the opportunity to study the interaction of aging and T1DM. The now expanded lifespan of patients with T1DM, owing in part to the benefits of intensive therapy demonstrated by DCCT/EDIC, means that patients with T1DM will increasingly be exposed to the generic effects of aging. Aging-sensitive dysfunction and disease, including cognitive dysfunction/dementia, physical dysfunction/frailty, affective disorders, specifically depression, and bone loss and osteoporosis have not been well studied in middle-aged patients with T1DM. Yet, cognitive dysfunction and physical frailty represent issues of great importance to aging patients and their care-givers, and have a major impact on quality-of-life and the personal and societal costs of diabetes.

The next phase (2017-2022) of EDIC will focus on the interaction between and the effects of aging and long-duration diabetes on cognitive and physical function and affective disorders (depression). The deep phenotyping and genotyping of the DCCT/EDIC cohort over more than 30 years will allow characterization of risk factors over time. In addition, as more severe, long-term complications accrue, we will characterize the risk factors and mechanisms that affect and predict severe complications.

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2. OBJECTIVES 2017-2022 (EDIC years 24-28)

The clinical research questions that have been addressed during EDIC, and will **continue** to be addressed, with a greater focus on epidemiology, include:

1. What is the modern-day clinical course of diabetic complications including the interactions among complications and co-progression of complications? Does intensive therapy only delay or does it actually prevent the development of advanced complications?
2. What are the pathophysiologic and pathogenic mechanisms that underlie the development and progression of microvascular and neurologic complications?
3. What are the long(er) term effects of the DCCT interventions on advanced complications?
4. What are the long(er)-term effects of intensive vs. conventional therapy on cardiovascular events?
5. What are the pathophysiologic, pathogenic and inflammatory mechanisms that underlie the development and progression of cardiovascular disease?
6. What is the continued longevity of the metabolic memory phenomenon?
7. What is the impact of intensive compared with conventional therapy on quality of life?
8. What are the economic (cost:benefit) implications of intensive therapy in the long-term?

During 2017-2022 (EDIC years 24-28), DCCT/EDIC will also address a **new set of questions**. The proposed aims capitalize on the multi-year investment in DCCT/EDIC and take advantage of one of the most valuable resources in the history of type 1 diabetes research. The highly characterized cohort remains extraordinarily loyal with 94% of the surviving cohort continuing to participate actively (see Section 5.6). They are now reaching the age and duration of diabetes where important and debilitating diseases occur. Although DCCT/EDIC has provided an abundance of seminal observations that underlie modern-day therapy and that have led to improvements in the long-term health of T1DM patients, T1DM is a life-long disease and requires life-long study. The proposed projects will utilize the traditional DCCT intention-to-treat (ITT) approach and, increasingly, epidemiologic (EPI) analyses. Some aims will be addressed by analyzing data previously collected using "*new analyses*", while others will utilize "*new measurements*" of already collected biological samples or "*new procedures*".

2.1   Aim 1: Examine the prevalence of cognitive, affective, and physical impairments in T1DM, and the association of DCCT treatment arm, glycemia, and established and putative non-glycemic risk factors on important domains of aging: cognitive, affective and physical impairments, functional limitations, disability, quality-of-life, frailty, falls, bone quality, fractures, and survival. At the beginning of the next study period, the cohort will have a mean age of 58 years and 40% of the cohort will be older than 60 years. EDIC subjects will be reaching the age where cognitive and physical deficits become prevalent in the general population, and may be accelerated in diabetes. *New procedures* include validated measures of cognition and sense of well-being and of physical function, frailty and bone mass. Understanding the effects of metabolic control, current and previous hypoglycemia and other factors on these outcomes, using ITT and EPI analyses, will facilitate our understanding of aging processes in T1DM and identify potential new targets for intervention.

2.2   Aim 2: Analyze the risk factors/mechanisms associated with severe/advanced microvascular complications. An event-driven strategy (performing risk factor analyses only after enough cases to provide adequate power have occurred) will be employed. As advanced microvascular events (e.g., blindness and renal failure) occur in the setting of mean duration of diabetes approaching 40 years, *new analyses* (both EPI and ITT) can be performed building on the phenotyping and genotyping already completed. *New procedures*, specifically ocular

coherence tomography (OCT) and *new measurements* of kidney dysfunction on stored samples, will be performed, providing information on retinal architecture and on new pathways of diabetic kidney disease. *New analyses* will include expansive modeling and mediation analyses to identify novel risk/protective factors, potential mechanisms and interactions among glycemic and non-glycemic risk factors.

2.3   Aim 3: Analyze the risk factors/mechanisms associated with CVD and mortality. Mortality is projected to reach 100 cases in the conventional treatment group during the study period and CVD cases will increase. Risk factors regarding recurrent CVD events and differences in risk factors for fatal vs. non-fatal events will be investigated. The same event driven strategy, *new analyses* and modeling will be employed as in **Aim 2**.

2.4   Aim 4: Develop new research approaches to measure the progression of diabetes outcomes (vectors) in T1DM, derived from the unique long-term, longitudinal follow-up of the DCCT/EDIC cohort. These *new analyses* will establish the rate of progression of individual complications, and the effects of the rate of development/progression of microvascular complications on each other, on CVD, and *vice versa*. Data-driven recommendations regarding appropriate frequency of screening for complications will be developed.

2.5   Aim 5: Study the long-term economic consequences of T1DM. This cross-cutting aim will assess the costs of diabetes treatments and of the expensive advanced complications that are developing, and validated measures of functional status and quality-of-life to assess the longer-term cost-effectiveness of intensive vs. basic therapy from health system and societal perspectives, and to assess the impact of health insurance and access to care on the processes and outcomes of care.

Operational objectives. In addition to the primary study objectives, operationally we will continue to:
1. Follow as many of the surviving DCCT/EDIC participants as possible.
2. Maintain acceptable levels of adherence to the visit and data collection schedule.
3. Monitor and maintain the precision, quality and accuracy of the assessments.
4. Analyze and disseminate the data promptly.
5. Encourage and implement new initiatives, resources permitting, which expand scientific productivity that emanates from the DCCT/EDIC cohort, its historic database, and banked biological samples. The inclusion of potential ancillary studies, as funding permits, will complement the Core protocol. As in the past, the potential impact of additional study measures on the subject cohort and staff will be taken into consideration.

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3. STUDY POPULATON

3.1   Recruitment

The DCCT was comprised of 1,441 research subjects with T1DM who were recruited between 1983 and 1989 to participate in a randomized clinical trial to examine the effects of intensive compared with conventional diabetes treatment on the development and progression of early microvascular, neurologic and other complications. In 1994, 96% of the surviving cohort agreed to participate in the EDIC study (**Table 1)**. At the end of EDIC year 22, 94% of the surviving cohort continues to be actively involved in the study.

All DCCT/EDIC participants will be invited to continue follow-up in EDIC. Although retention of the original DCCT cohort has remained very high during the previous 23 years of EDIC, with no appreciable loss to follow-up, the Research Group will not take continued participation for granted.

Table 1. Participant retention* in DCCT/EDIC

Year	Phase	Participants (n)	Retention (%)
1983-90	DCCT baseline	1,441	100
1993	DCCT closeout	1,422	99
1994	EDIC baseline	1,375	96
2003	EDIC year 10 end	1,354	97
2008	EDIC year 15 end	1,297	95
2016	EDIC year 22 end	1,214	94

* Number and percent of the original surviving DCCT cohort actively participating in the study (see Section 5.6). Loss to follow-up includes 11 deaths during DCCT (1983-93) and 133 deaths during EDIC follow-up (1994-2017).

Any new procedures in the protocol will be explained in detail to participants and informed consent obtained. The duration of EDIC follow-up has been extended based on competitive funding applications. The most recent 5-year extension is for the period July 1, 2017 through June 30, 2022.

3.2   Informed Consent

To be eligible for the continuing follow up study, each participant must be willing to sign a statement of informed consent to document understanding of the continued study and its procedures, risks and benefits, and agreement to participate in the study activities. The consent process will include provision of written information and person-to-person discussion with potential volunteers to discuss the project further and address any questions or concerns. Since many of the elements of the Core protocol are very similar to the DCCT and EDIC tasks that the study cohort has been performing for as long as 33 years, this process should be relatively straightforward.

Clinic staff, including the Principal Investigator and Study Coordinator, will participate in the consent process. In accordance with DHHS policy on informed consent, it is necessary to recognize that each subject's 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 consent. Individual Clinical Centers may require that the recommended Informed Consent Form be amended to include additional statements or be reworded based on local institutional requirements.

The Informed Consent will be signed and maintained in the participant's research record at each EDIC center, and must be signed before any additional data can be collected on that

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participant. As with the informed consent process during the past 33 years of DCCT/EDIC, volunteers will be able to decline participation in specific elements of the study, but continue to participate in the Core study.

3.3   Demographics

The DCCT population, aged 13-39 years at entry in 1983-89, included two cohorts selected to answer two separate questions. The primary prevention cohort was selected to determine whether intensive diabetes treatment, designed to achieve glucose goals as close to the non-diabetic range as possible, would prevent the development and subsequent progression of retinopathy in T1DM patients with short (1-5 y) duration, no retinopathy and <40 mg albuminuria/24h at baseline. The secondary intervention cohort was selected to determine whether intensive therapy would affect the further progression of retinopathy in T1DM patients with 1-15 y duration, minimal to moderate retinopathy and <200 mg albuminuria/24h at baseline. Thus, the two cohorts were selected to have either no or minimal complications at baseline. In addition, the entry criteria eliminated patients with hypertension (≥140/90 mm Hg), hyperlipidemia (total cholesterol >3SD over Lipid Research Center (LRC) age and gender specific norms), known cardiovascular disease, and patients who were unlikely to accept randomization or comply with the highly complex protocol. The characteristics of the cohort at the end of EDIC year 22 are summarized in **Table 2**.

3.4   Retention

As of May 2017, the EDIC follow-up study has spanned ~23 years and the total mean follow-up of the original cohort is approximately 30 (range 27-34) years. Retention of the DCCT cohort has remained outstanding. Ninety-six percent of the surviving DCCT cohort joined EDIC in 1994 and 94% of the original surviving cohort (n= 1,214 of 1,297) have remained active in EDIC at the end of year 22 (**Table 1**).

All reasonable efforts will be made to encourage continued study participation by all participants. In-person visits, completed by EDIC certified staff, within defined visit windows are preferred, and all reasonable efforts to have such visits will be made by the clinical staff at each EDIC Clinical Center. Visit windows are defined as 4 months on either side of the participant's DCCT randomization anniversary. If a scheduled visit does not take place, the visit will be re-scheduled as soon as possible, ideally within the defined visit window. Alternatives to an in-person visit will be arranged on a case-by-case basis for those occasions when a participant is unwilling, or unable to travel to an EDIC Clinical Center. Alternatives to an in-person EDIC visit include:

- Phone / electronic visit (e.g. email, video conference)
- Combined biennial visit
- Modified visit schedule
- Home visit to the participant (if allowed by the local institution and acceptable to the participant)
- Capillary (fingerstick) HbA1c collection in the home setting, with analysis by the central EDIC laboratory.
- Medical records request

Table 2. Characteristics of EDIC study population at the end of EDIC year 22 of follow-up (April 2016) by original cohort assignment

	Primary Prevention	Secondary Intervention	Total
N	**611**	**603**	**1,214**
Attained age (years)	56 ± 7	58 ± 7	57 ± 7
Gender (% males)	52	52	52
Diabetes duration (years)	32 ± 2	39 ± 4	35 ± 5
Race (% white)	96	97	97
Retinopathy (%)*			
PDR or worse or scatter laser	18	36	27
CSME or focal laser	17	28	22
Any Laser therapy	19	35	27
Blind either eye (worse than 20/200)	<1	2	1
Nephropathy (%)**			
AER ≥300 mg/24 h	5	5	5
Macroalbuminuria or sustained eGFR<60	8	9	8
Sustained eGFR<60 ml/min/1.73 m^2 or ESRD	5	6	6
eGFR <60 ml/min/1.73 m^2 or ESRD	6	8	7
eGFR <30 ml/min/1.73 m^2 or ESRD	3	2	3
Any dialysis or transplant	2	2	2

Data are mean ± SD or %.
NPDR, non-proliferative diabetic retinopathy; CSME, clinically significant macular edema; HRC, high risk characteristics; AER, albumin excretion rate.
* Current retinopathy based on the year 19-22 cycle of fundus photography (n=1,123).
** Current nephropathy based on the year 21/22 cycle of renal assessments (n=1,143)

Local regulations, resources, and individual participant considerations will be used to determine the most appropriate visit type. When a participant moves into a geographic area served by a Clinical Center other than the one to which he/she was originally enrolled or is currently being followed, the participant will be asked to consider transfer to the closer center. Issues such as participant willingness to transfer, proximity to new center, transportation difficulties, participant health, travel time and cost will be considered.

Regular direct communication between the center and the participant will be maintained by telephone, letter, newsletter, and other adherence techniques. Central retention efforts include:

- The EDIC newsletter is compiled semi-annually by EDIC study coordinators and has as its stated purpose to: "…provide you with important information as an EDIC participant and as a person living with Type 1 diabetes." For the scholarly publications, the public EDIC website allows participants to review the publication list.
- The EDIC Supply Committee arranges for donated supplies of insulin, blood glucose meters, strips, glucose tablets and syringes, and discounts from pump vendors to be used to acknowledge annual participation.
- "Searching for lost participants" is a resource that provides lists of internet-based mechanisms (acceptable by most institutional IRBs) to ensure that clinics can search for any participants that have become difficult to find over time.
- For participants who must travel >100 miles one way to the Clinical Center, the Clinical Coordinating Center (CCC) provides central reimbursement to support participant travel (mileage, meals, airfare or hotel accommodation) for an annual visit as needed. For those residing less than 100 miles one-way, but who need support for travel, reimbursement is provided from local Clinical Center budgets.

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3.5   Inactive Status / Lost to Follow-up

Transfer to inactive status is defined as a moratorium on subject participation in any EDIC study assessments. If the participant withdraws consent, clinic staff are precluded from initiating contact with the participant. Transfer to inactive status is allowed in the following situations:

- When in the judgment of the Principal Investigator and Study Coordinator, any manner of participation in the study would be directly injurious to the participant's well-being or could no longer be considered informed;
- Inability to obtain any annual determinations, including persistent inability to obtain any information from the participant by any means, for two consecutive years;
- Participant withdraws consent for continuing participation in the study.

Participants who may be considering withdrawing consent to participate in EDIC should be provided with information about alternatives to complete withdrawal, as noted above, so as to continue some level of participation. An inactive participant becomes active whenever he or she returns to some level of study participation. Participants who have formally withdrawn consent may also resume participation at any time, and will be required to sign the most current version of the EDIC consent document before any EDIC assessments can be completed.

The designation "Lost to Follow-Up" can only be assigned at the conclusion of the study or upon death. Ongoing efforts will be employed to keep the number of participants designated as lost to follow-up at the conclusion of EDIC to a minimum.

4. STUDY PROCEDURES

The EDIC study will continue as a non-interventional, observational follow-up of the DCCT cohort. Study personnel will not provide diabetes or any other medical care as part of the study. All medical care will be provided by the participants' local care providers. Of note, as of December 2015, approximately 26% of the study cohort receives diabetes care at a DCCT/EDIC Clinical Center, but not as part of the study, and not necessarily from prior or current DCCT/EDIC staff.

During the course of the study, participants will be asked to undergo a set of standardized procedures on a scheduled basis. Visits will be scheduled annually, based on the DCCT randomization date, to optimize convenience for the study participants, maximize efficiency and minimize costs.

The core methods and procedures have been selected with the aim of being able to complete the annual visit in a single day. Although local and individual factors, such as travel distances, may occasionally require an overnight stay, we expect this to be the exception. The more time-consuming and/or laborious elements of the protocol will be staggered when possible, for example in alternate years, to distribute the workload for participants and staff. Self-administered questionnaires can be sent to the participants before their scheduled visits to reduce the amount of time needed during the visit. The methods for the 2017-2022 study period are summarized below. Procedures involving repeated measures over time aim to employ consistent measurement techniques, as appropriate. The schedule of outcome measures is shown in **Table 3**.

4.1   Standardized History and Physical Examination: The information collected annually through the standardized history and physical examination addresses general health, current medication use, and diabetes-specific outcomes. The same questionnaire and physical examination, with minor modifications, has been employed throughout the DCCT and EDIC, facilitating longitudinal study. The history and physical examinations are completed by qualified and certified DCCT/EDIC staff.

4.2   Blood Glucose Control: Annual HbA1c measurements will be collected at the Clinical Centers and processed at the Central Biochemistry Laboratory.

4.3   Questionnaires: The questionnaires, directed at measuring overall health status, insurance status, diabetes-related quality-of-life (DQOL), and self-reported visual function (NEI-VFQ) data have been used during DCCT and EDIC and have been described in detail in the past. New questionnaires addressing quality of life, well-being, cognitive and physical function, frailty and affective disorders (depression) have been added. The questionnaires include:
- Health Care Delivery questionnaire
- Diabetes Quality of Life (DQOL) questionnaire
- 36-Item Short Form Health Survey (SF-36) questionnaire
- Quality of Well Being Self-Administered (QWB-SA)* questionnaire
- EuroQOL (EQ-5D) questionnaire
- National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)

4.4   Retinopathy: Seven-field stereoscopic fundus photography and evaluation of intraocular pressure and visual acuity have been performed by DCCT/EDIC certified ophthalmologists and photographers from the outset of the DCCT. An ophthalmologic exam, visual acuity, seven-field stereoscopic fundus photography, and ultrawide field photographs and ocular coherence tomography (new assessments) will be completed once during the next 5-year

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study period. The grading of the OCT and fundus photos will be conducted at the Central Ophthalmologic Reading Center (CORU).

4.5   Nephropathy: The nephropathy evaluation has been consistently applied using standardized methods throughout DCCT and EDIC. Procedures will include a random urine collection for measurement of urinary albumin and creatinine which will continue to be used to calculate albumin creatinine ratio (ACR); serum creatinine and calculated eGFR will continue to be measured annually.

4.6   Neuropathy: The Michigan Neuropathy Screening Instrument (MNSI), a history and physical examination-based instrument, has been validated as a reliable index of peripheral neuropathy in other studies and has been validated within EDIC against the DCCT/EDIC outcome of "confirmed" clinical neuropathy as a measure of peripheral neuropathy. The MNSI will continue to be completed annually and will be an important covariate in the assessment of fall risk.

4.7   Cardiac Autonomic Neuropathy (CAN): Based on R-R interval measurement, a formal CAN testing protocol has been repeated to measure progression of autonomic neuropathy and as a risk factor for CVD. This evaluation was last performed in 2009-2010. There are no plans to repeat formal CAN assessments as previously performed. The annual medical history will continue to ask about the presence of autonomic symptoms. In addition, new analyses of previously-collected and future ECG's are proposed to derive surrogate measures of CAN presence, severity and progression.

4.8   Cardiovascular Disease (CVD): The Core elements of the CVD outcomes will remain the same as during DCCT/EDIC, with some changes in frequency, including annual history and physical data addressing the occurrence of intercurrent events (validated and confirmed by the Morbidity & Mortality Committee), ankle:brachial index (collected annually through September 2012, and on alternate years thereafter), annual ECG, and alternate year fasting lipids (total, HDL and LDL cholesterol, and triglycerides). Ankle:brachial index will be measured one time during the next study period. Biomarkers for heart failure (such as NT-proBNP and hsTroponinT) will be measured annually using samples obtained from the alternating year renal and lipid measures.

4.9   Cognitive Function and Affective Disorders (Depression): Previously completed cognitive assessments will be utilized and new measures added (* indicates measures previously completed during DCCT/EDIC). These measures will be completed twice during this study period.
- Subset of tests from the original DCCT/EDIC Neuropsychological test battery within the domains of immediate memory and psychomotor efficiency*
- Montreal Cognitive Assessment (MoCA)
- Subset of tests from the NIH Toolbox
- Cognitive Change Index Self-Report (CCI-SR) questionnaire
- Symptom CheckList-90-Revised (SCL-90R)* questionnaire
- Patient Health Questionnaire-9 (PHQ-9)

4.10   Physical Function: Assessment of physical function and frailty will be performed once during the 5-year period (* indicates measure previously completed during DCCT/EDIC).
- Disabilities of the Arm, Shoulder and Hand (DASH)* questionnaire
- NHANES Physical Function and Disability questionnaire
- International Physical Activity Questionnaire Short-Form (IPAQ-SF)
- Short Physical Performance Battery (SPPB)

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- Goniometry measure of shoulder flexion
- Grip strength
- Reaction time
- Annual self-reported history of falls and fractures

4.11   Skeletal Health: Measures of bone density and fractures along the spine will be obtained using dual x-ray absorptiometry (DXA) scanning. In a subset of clinics, HR-pQCT (High Resolution-peripheral Quantitative Computed Tomography) scans will also be performed measuring the 3-dimensional (3D) microscopic shape of the bones. These scans will be performed cross-sectionally during EDIC years 24-25. The Block Food Frequency Questionnaire (BFFQ) will be used to assess calcium and vitamin D dietary intake.

4.12   Urologic and Sexual Function: Confidential self-completed questionnaires will continue annually to assess symptoms and perceptions regarding urologic symptoms and sexual function.

4.13   Biomarkers and Risk Factors: Numerous biomarkers have been measured over time in EDIC and are available for analyses. Biosamples will continue to be collected over time that will be used for analyses for various cardiac biomarkers during this study period.

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Table 3. Schedule of follow-up examinations

EDIC Year (Calendar years of visit)	24 (2017-18)	25 (2018-19)	26 (2019-20)	27 (2020-21)	28 (2021-22)
Medical History					
Updated health history	X	X	X	X	X
Current medications	X	X	X	X	X
Laboratory Measures					
HbA1c	X	X	X	X	X
Fasting lipids	½	½	½	½	½
Urine albumin and creatinine	½	½	½	½	½
Serum creatinine	X	X	X	X	X
hs-Troponin	X	X	X	X	X
N-terminal pro b-typenatriuretic peptide	X	X	X	X	X
Physical Examination					
Weight, height, waist	X	X	X	X	X
Blood pressure, pulse	X	X	X	X	X
Electrocardiogram	X	X	X	X	X
Ankle:brachial index by Doppler			X		
Questionnaires					
Health Care Delivery	X	X	X	X	X
Diabetes Quality of Life (DQOL)		X		X	
36-Item Short Form Health Survey (SF-36)		X		X	
Cognitive Change Index (CCI-SR)	½	½		½	½
Symptom CheckList-90 (SCL-90R)	½	½		½	½
Patient Health Questionniare-9 (PHQ-9)	½	½		½	½
Disability of Arm, Shoulder, Hand (DASH)	½	½			
NHANES Physical Function & Disability	½	½			
International Physical Activity (IPAQ-SF)	½	½			
Quality of Well-Being (QWB-SA)	½	½			
EuroQol (EQ-5D)	½	½			
Block Food Frequency (BFFQ)	½	½			
Urologic Complications	X	X	X	X	X
Microvascular Outcomes					
Optical coherence tomography (OCT) Fundus photography		⅓	⅓	⅓	
Visual acuity, intraocular pressure		⅓	⅓	⅓	
National Eye Institute Visual Function-25 (NEI-VFQ-25)		⅓	⅓	⅓	
Michigan Neuropathy Screening Instrument (MNSI), 10 gm filament examination	X	X	X	X	X
Aging Batteries and Assessments					
DCCT/EDIC Neuropsychological Subset	½	½		½	½
Montreal Cognitive Assessment (MoCA)	½	½		½	½
NIH Toolbox Subset	½	½		½	½
Short Physical Perform. Battery (SPPB)	½	½			
Goniometry measure of shoulder flexion	½	½			
Grip Strength	½	½			
Reaction time	½	½			
DXA scan	½	½			
Adjudicated Events					
Cardiovascular disease	X	X	X	X	X
Dialysis or kidney transplant	X	X	X	X	X
Death	X	X	X	X	X

X = All EDIC participants will be evaluated.
½ and ⅓ = One half or one third of the EDIC participants will be evaluated for this measure, so that every two or three years a completed cohort is evaluated.

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5. STUDY STRUCTURE

The previously established organizational structure of the EDIC, which was developed to coordinate the activities of the necessary committees, laboratories, units and review groups, and to facilitate the conduct of this study by ensuring careful and uniform adherence to the Protocol and Manual of Operations, will continue.

The study is sponsored by the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK). The Observation Study Monitoring Board (OSMB), whose members are selected by the NIDDK and independent of the conduct of the study, consists of experts in clinical diabetes, epidemiology, data management, and statistics to review the progress of the study periodically and advise the NIDDK and the Research Group. The OSMB monitors the Core study as well as the EDIC ancillary studies, importantly providing a collective perspective of Research Group progress.

5.1   Research Group: The Research Group is the representative body of all study staff and provides overall scientific direction for the study through consideration of recommendations from the working committees. It is comprised of a Chair / Vice-chairs, the Principal Investigator and Study Coordinator from each of the Clinical Centers, the Principal Investigator and Director of the Data Coordinating Center (DCC), the Principal Investigator of the Clinical Coordinating Center (CCC), and the Project Scientist and Program Director from the NIDDK Diabetes, Endocrinology, and Metabolic Diseases Program Office. The Research Group and its ancillary study collaborators meet once a year preceding the American Diabetes Association meeting.

5.2   Executive Committee: The Executive Committee acts on behalf of the Research Group during the intervals between Research Group meetings and makes the day-to-day management decisions needed for the study to proceed in a smooth, efficient, and orderly way. The Executive Committee is comprised of the Chair / Vice-chairs of the Research Group, the Principal Investigator and Director of the Data Coordinating Center, the Principal Investigator of the Clinical Coordinating Center, the Project Scientist and Program Director from the NIDDK Diabetes, Endocrinology, and Metabolic Diseases Program Office, and Co-chairs of the Study Coordinators Committee. The Executive Committee develops policies and procedures for the Research Group, and ensures that these policies are properly implemented. Major decisions that may affect the integrity of the study or require a protocol change will be made only after consideration by the Research Group and approval by the majority of voting members, in-person or via electronic communication.

5.3   Clinical Centers: There are 27 Clinical Centers that will continue to participate in the EDIC Study (**Table 4**). The Clinical Centers are staffed by a Study Coordinator and other necessary personnel, including junior Co-Investigators, under the supervision of a Principal Investigator. The Principal Investigator, Co-Investigator and Coordinator will work with the Data and Clinical Coordinating Centers, the Executive 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 responsible for maintaining contact with all participants and conducting all EDIC core activities as described in the protocol and Manual of Operations. The Clinical Centers will also facilitate the conduct of all approved EDIC ancillary studies. Junior Co-Investigators are certified to assist with participant visits, encouraged to participate in committee work (see Section 5.7), and assigned to manuscript writing teams.

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5.4   Clinical Coordinating Center: The Clinical Coordinating Center (CCC), located at Case Western Reserve University, provides overall coordination of all fiscal aspects for the Clinical Centers, manages protocol implementation, and oversee all aspects of the 27 Clinical Centers' performance. The CCC manages subcontracts with each of the EDIC Clinical Centers and manages budget preparation for and invoice processing from all Clinical Centers. In addition to the core budgets, the CCC works closely with collaborators of ancillary studies to anticipate study-wide Clinical Center needs and prepare ancillary study budgets. The CCC provides support to clinical centers during periods of staff transition or difficult periods of protocol implementation and helps to determine study-wide clinical requirements and identify institutional resources. Given the longevity of the EDIC Study and the focus on participant retention, anticipation of EDIC Clinical Center staff transitions is monitored proactively by the CCC through periodic surveys on succession plans for the Principal Investigators and Study Coordinators. This encourages Clinical Centers to prepare for transitions. Principal Investigators are encouraged to seek junior investigators with special interests and expertise in the complications of diabetes. Through this process, training of junior investigators and coordinators in the EDIC protocol(s) occurs smoothly, typically through junior Co-Investigators joining one year prior to transition, and overlap of current and succeeding coordinators for at least 2-4 weeks. The CCC works closely with the NIDDK, the study Chair/Vice-chairs, the Data Coordinating Center, and the EDIC Clinical Center staff to smoothly integrate the fiscal and technical aspects of EDIC. The CCC and DCC communicate regularly between committee meetings to review progress and issues.

5.5   Data Coordinating Center: The Data Coordinating Center (DCC), located at the George Washington Biostatistics Center, participates in all aspects of the design and implementation of and adherence to the EDIC study protocol, provides scientific, technical and staff services to the Research Group and each of its working committees/groups, implements and maintains the systems necessary for data collection, editing, management, and statistical analysis, and maintains permanent study records and files. The DCC is responsible for providing appropriate and timely data reports to the Executive Committee, the Observation Study Monitoring Board (OSMB), the NIDDK, and the External Evaluation Committee (EEC), when convened by the NIDDK. The DCC and CCC work together to develop and implement core studies and facilitate numerous ancillary studies, including conducting relevant training and certification of study staff. The DCC and CCC are responsible for the planning and logistical coordination of meetings of the Research Group and Study Coordinators, as well as for the logistical coordination of the OSMB and any External Evaluation (EEC) meetings.

5.6   Central Units: There are currently three Central Units that operate under subcontract to the DCC and include: Central Biochemistry Laboratory, Central Ophthalmologic Reading Center and Central ECG Reading Unit. A Central Neuropsychological Reading Center and Bone Reading Unit will be contracted during 2017-2022. These central units are responsible for providing study data and analysis of participant evaluations, as well as scientific and technical guidance to the Research Group, specific working committees, and the DCC. The Data Coordinating Center is responsible for the movement of study generated materials from the Clinical Centers to the Central Units and subsequently to the NIDDK Repository.

5.7   Working Committees: The Working Committees include the: Adherence Monitoring Committee, Data Quality Assurance Committee, Publications and Presentations Committee, Publications Working Group, Research Review Committee, Mortality and Morbidity Review Committee, and Study Coordinators Committee. Committee members are appointed by the Executive Committee from among the professional personnel from each of the Clinical Centers, the Data and Clinical Coordinating Centers staff, the NIDDK staff, and necessary consultants.

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The members of the Executive Committee are *ex-officio* members of each of the working committees. Additional complications-based working groups (e.g. ophthalmology, renal, cardiovascular) are comprised of Research Group members plus outside experts in the principal outcomes of DCCT/EDIC.

Table 4. EDIC Clinical Centers

Number	Name	City, State
1	Case Western Reserve University	Cleveland, OH
2	University of Pennsylvania	Philadelphia, PA
3	Cornell University	New York, NY
4	Henry Ford Health System	Detroit, MI
5	Joslin Diabetes Center	Boston, MA
6	Massachusetts General Hospital	Boston, MA
7	Mayo Clinic	Rochester, MN
8	Medical University of South Carolina	Charleston, SC
9	International Diabetes Center	Minneapolis, MN
10	University of Iowa	Iowa City, IA
11	University of Minnesota	Minneapolis, MN
12	University of Missouri	Columbia, MO
13	University of Pittsburgh	Pittsburgh, PA
14	University of Tennessee	Memphis, TN
15	University of Texas	Dallas, TX
16	University of Toronto	Toronto, Ontario, Canada
17	University of Washington	Seattle, WA
18	University of Western Ontario	London, Ontario, Canada
19	Vanderbilt University	Nashville, TN
20	Washington University St. Louis	St. Louis, MO
21	Yale University	New Haven, CT
23	Northwestern University	Chicago, IL
24	University of California San Diego	La Jolla, CA
25	University of Maryland Baltimore	Baltimore, MD
26	University of New Mexico	Albuquerque, NM
27	University of South Florida	Tampa, FL
41	University of Michigan	Ann Arbor, MI

Effective September 1, 2012, Albert Einstein College of Medicine (clinic 22) was closed and participants were given the option to transfer to another conveniently located Clinical Center.

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Figure 3. Organizational structure of the EDIC study

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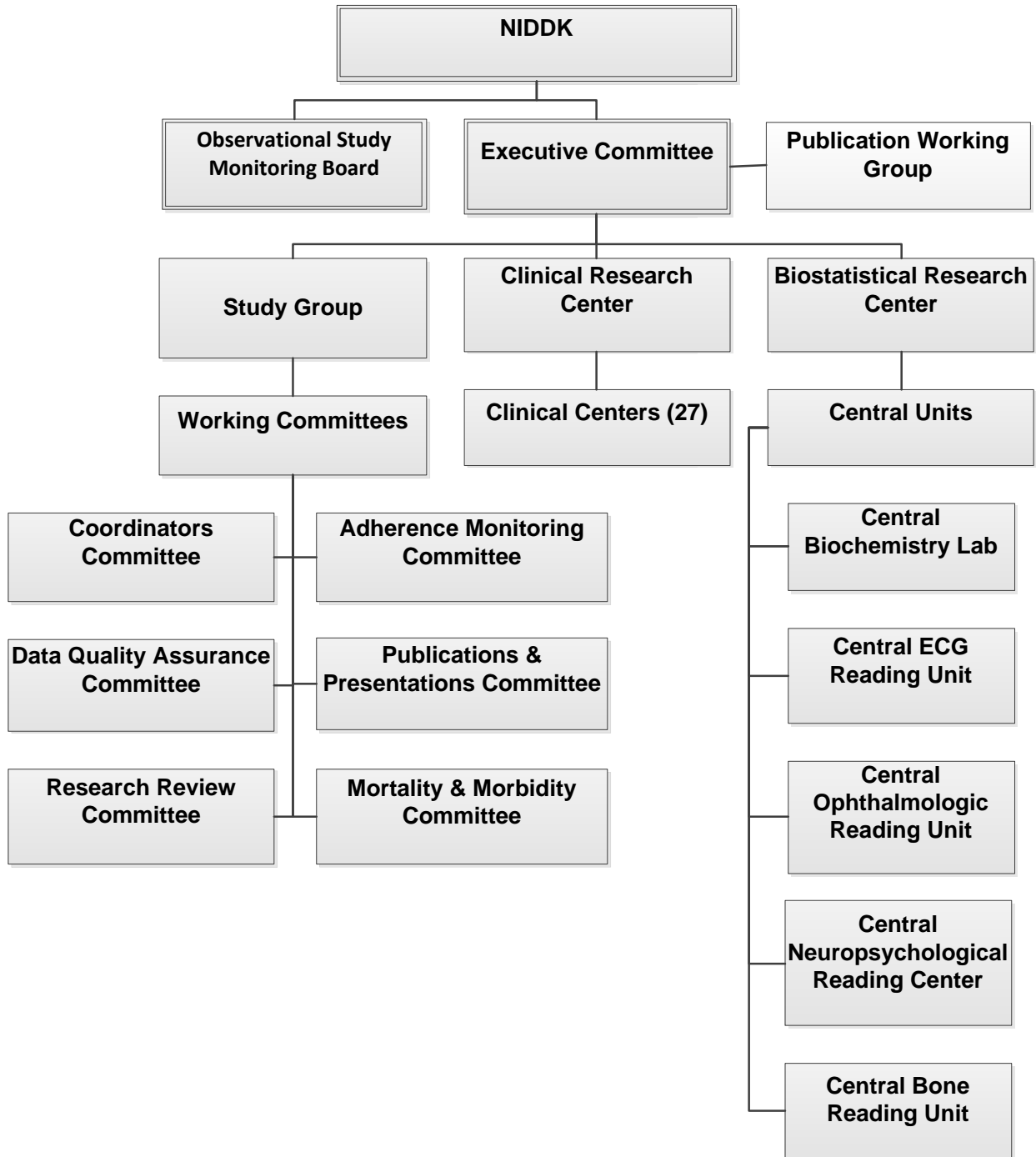
6. STUDY POLICIES

The policies and procedures specific to publications and presentations, authorship, ancillary studies and external collaborations involving the DCCT/EDIC study, protocol changes, and transfer of DCCT/EDIC biosamples and data to the NIDDK Repository are summarized below.

6.1   Editorial Policy

The "DCCT/EDIC Research Group" is used when referring to or citing the DCCT/EDIC Research Group in publications and presentations of the DCCT/EDIC study. The Publications and Presentations (P&P) Committee will assume responsibility for arranging the preparation of all press releases, interviews, presentations, and publications relating to the study. The P&P Committee will review and monitor content development, preparation and review of all manuscripts. Recommendations will be presented to the Executive Committee and Research Group for approval.

6.2   Publications Working Group

The Publication Working Group (PWG), composed of the study leadership, such as the Study Chair, the Principal Investigator and Director of the Data Coordinating Center, the Chair of Publications and Presentations Committee, the Principal Investigator of the Clinical Coordinating Center and one of the Co-chairs of the Study Coordinators Committee, is responsible for reviewing and coordinating proposals for publications and presentations. The PWG provides the study-wide vision of the progress of the study, knowledge of the provenance of topics and the workings of our collaborations, ancillary and sub-studies, content expertise, and knowledge regarding historic/recent/current involvement of Research Group members in publication and presentation activities.

6.3   Publications and Presentations Duties and Policies

The Publications and Presentations (P&P) Committee will: recommend policy and procedures for review and approval of all communications (written and spoken) regarding the study to outside groups; monitor the writing of each paper to ensure timely publication; establish standards of excellence for publications; review, edit and approve all publications and presentations prior to submission; review any publications arising from ancillary studies; suggest appropriate journals for publications and monitor the process of publication, and; perform other writing, reviewing, or editing tasks assigned by the DCCT/EDIC Research Group or the Executive Committee. Manuscript reviews will be conducted following editorial policy guidelines to:

- Ensure that all publications preserve the scientific integrity of the study
- Maintain the highest standards in the preparation of presentations and publications
- Correct factual and conceptual inaccuracies if necessary
- Safeguard the rights of volunteer participants
- Prepare comments to assist collaborating scientists in publishing papers of the highest quality and clarity
- Inform the Executive Committee, Research Group, NIDDK, and external EDIC advisory groups of all public dissemination of information about the study and coordinate press releases with the NIDDK
- Avoid conflict with and/or duplication of other publications
- Coordinate the releases of major study data with NIDDK

6.4 Authorship

The DCCT/EDIC study has evolved from a randomized controlled clinical trial to an observational study of individuals with T1DM. In addition, we have developed numerous broad based collaborations with investigators outside of the DCCT/EDIC Research Group who are making unique contributions to our understanding of T1DM and its associated complications. Responsibility for the category assignment for all manuscripts will rest with the Publications Working Group in consultation with the Executive Committee. The categories of papers are classified based on the following authorship principles:

6.4.1   Primary Outcome Manuscripts (Category 1): These manuscripts address the major primary outcomes of the DCCT/EDIC study. The authorship is the DCCT/EDIC Research Group. The writing team for these papers is identified in the manuscript. The complete list of DCCT/EDIC investigators appears as part of the manuscript, usually in an appendix at the end of the manuscript, as negotiated with the publishing journal.

6.4.2   Other Outcomes Manuscripts (Category 2): These manuscripts report various analyses of complication outcomes, metabolic intermediates and biomarkers, or natural history of T1DM that utilize the database from the entire cohort. This category will represent the majority of the manuscripts. These manuscripts also include sub-studies and ancillary studies conducted as additional initiatives beyond the initial DCCT/EDIC protocol. The authorship will be the writing group: Chairperson, authors A, B, C, etc. and the DCCT/EDIC Research Group.

6.4.3   Miscellaneous Manuscripts (Category 3): These manuscripts generally focus on methodological issues and may include results of subgroup analyses that do not include data from the entire DCCT/EDIC cohort. Authorship includes named authors A, B, C, etc.; the DCCT/EDIC Research Group is acknowledged in the manuscript but not included as a named author.

6.5 Ancillary Studies

Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the EDIC. Ancillary studies that complement the objectives and thereby enhance the value of the EDIC study are encouraged. Such studies should augment and promote the continued interest of both participants and investigators. To protect the integrity of the EDIC study, a proposal to conduct an ancillary study must be reviewed and approved by the Executive and Research Review Committees followed by the Research Group before its initiation. All approved ancillary studies will be self-funded and reviewed regularly for progress and impact on the EDIC study as a whole.

6.6 Protocol Changes

Major changes in the Protocol will be recommended by the Executive Committee or the Research Group only if they are required to ensure subject safety, will significantly enhance the scientific validity of the study or in response to fiscal constraints, assuming validated scientific data can justifiably support the change. To institute a major Protocol change, three-fourths of the Research Group must approve the change. The voting body for the EDIC study includes all Clinical Center principal investigators and coordinators, and one vote from the Data Coordinating Center, the Clinical Coordinating Center and the NIDDK scientific project officer for the EDIC study. For other protocol changes, only a simple majority is required.

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6.7   Consideration of Additional Procedures

During the continuing follow-up of the EDIC Study, the Executive Committee will consider proposals for Protocol changes that may originate from the NIDDK, the OSMB, the Data or Clinical Coordinating Centers, or one of the working committees. Groups can propose changes based on operational factors or the desirability of performing additional outcome measures.

6.8   Participation in Other Research Studies

As part of the informed consent process, all volunteers are asked to review potential participation in any other research projects in advance with the EDIC staff at their Clinical Center. Participation in research studies that involve the use of experimental agents that can interfere with the objectives of EDIC by affecting EDIC outcomes, or that may impair participation in EDIC or EDIC data collection is discouraged.

6.9   NIDDK Central Repository

Specimens and data transferred to the NIDDK Central Repository are de-identified prior to transfer. Should a participant decline continued sharing of his/her stored samples with the NIDDK Central Repository, they will be asked to submit their request to the Principal Investigator/Study Coordinator at their Clinical Center who will communicate this information to the Data Coordinating Center which will be responsible for implementing this request. Previously submitted samples are not able to be withdrawn from the NIDDK Repository.

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7. STUDY MONITORING / QUALITY CONTROL

The Research Group has instituted mechanisms for continuous performance monitoring and improvement of all study units. An overall study rate of follow-up of at least 90% of active participants is the goal. Monitoring the Clinical Centers remains centered on the principal operational goals of EDIC, which include 1) to retain as many EDIC participants as possible within the study, 2) to obtain as many of the outcome measurements as possible, and 3) to sustain as high a level of consistency and quality as possible in the collection and analysis of the data.

The Adherence Monitoring Committee and Data Quality Assurance Committee work with the Data and Clinical Coordinating Centers to monitor clinic performance with regard to subject retention and adherence to the protocol and Manual of Operations, and data integrity, reliability, and reproducibility.

The Adherence Monitoring Committee works with the Data and Coordinating Centers to closely monitor the implementation of all study protocols at all Clinical Centers. Quarterly conference calls review the accrual of each individual outcome measurement clinic by clinic. The EDIC goal for all data measurements is an overall average of 90% adherence among surviving subjects, with a minimum 80% adherence by any individual clinic. If an individual Clinical Center is faltering in obtaining core protocol data or implementing a new study (< 80% of expected data collection), the committee undertakes a comprehensive evaluation of the factors influencing that clinic's performance. A customized plan for improvement and follow-up is implemented.

External quality control surveillance programs established previously during DCCT/EDIC will continue. The quality control data from the central units are analyzed by the DCC and presented to the Data Quality Assurance Committee for review. Every 4 months, quality assurance summary measures are reviewed, and parameters such as inter- and intra-reader variability (e.g. fundus photos, CT scans), coefficients of reproducibility and reliability of split duplicate laboratory samples (e.g. HbA1c, lipids, and microalbuminuria), and re-read reproducibility for annual evaluations (fundus photos, ECGs) are assessed. The Data Quality Assurance Committee evaluates the research and/or clinical significance of variations over time and seeks to identify the source of variability which may include errors in collection, measurement or reporting. Any deficiencies detected will be investigated and corrections made to the database as indicated. In addition, Clinical Centers will be contacted to discuss clinic-specific quality issues, possible causes and intervention, when indicated. Selected data and overall error rates in the completion of data forms are monitored by the DCC and Data Quality Assurance Committee. As EDIC continues, any other data that are determined to be critical to the study will be monitored.

Advances in technology and availability of materials have necessitated changes in the collection and analysis processes and/or equipment over time in the DCCT/EDIC. Prior to implementation of any equipment or procedural change, reliability and reproducibility evaluations are conducted to ensure comparability of results. Examples include changes in assays and/or equipment at the Central Biochemistry Laboratory, the use of digital compared to film fundus photographs, and digital compared to paper ECG acquisition. Implementation of process changes is contingent on verification of data comparability.

The following is a summary of the quality assurance procedures for all study outcomes.

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7.1   Glycemia: Hemoglobin A1c (HbA1c)

HbA1c has been measured throughout DCCT/EDIC by ion-exchange high performance liquid chromatography (HPLC). The DCCT/EDIC Study in type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes, which aligned its glycated hemoglobin assay to the DCCT assay, have shown that intensive treatment of diabetes mellitus decreases the development and/or progression of long-term complications. Both the DCCT and UKPDS have also shown a strong correlation between HbA1c values and complications. The conclusions of these studies rest on long-term consistency of the HbA1c methods, now extending into a fourth decade in EDIC. The National Glycohemoglobin Standardization Program (NGSP) was founded by DCCT investigators and arose from the DCCT process of monitoring the consistency of HbA1c measurements in the Central Biochemistry Laboratory (www.ngsp.org/). Moreover, the NGSP has aligned all of the assays worldwide to the DCCT standard. More recently the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has complemented the NGSP in sustaining a program in which the CBL participates to optimize consistency of HbA1c assays within EDIC. The long-term stability of the HbA1c measurements underpins most of the conclusions of DCCT/EDIC and the study continues to contribute to the harmonization of this assay throughout the world.

7.2   Renal Markers

The evaluation of nephropathy has been consistently supported using standardized methods throughout DCCT and EDIC. Creatinine in serum and urine has been measured in DCCT/EDIC with highly stable methods, more recently with an enzymatic method standardized by isotope dilution mass spectrometry (IDMS). Modern equations have permitted an estimated glomerular filtration rate (eGFR) to be calculated from the concentration of creatinine in serum. Spot urine measurements of albumin related to urine creatinine are utilized to calculate albumin-to-creatinine ratio, to measure albuminuria.

7.3   Cardiovascular Risk Factors

The concentrations of lipids in serum have long been utilized as significant risk factors for cardiovascular disease. The CBL in DCCT/EDIC has consistently used well standardized methods, with accuracy verified by certification through the Centers for Disease Control (CDC) Lipid Standardization Program.   In addition to its broad and deep technical accomplishments, the CBL has the capability of measuring other markers of potential importance to assess the risk of CVD in the EDIC. A host of other established and putative CVD risk factors have been studied by DCCT/EDIC collaborators, all with validated standardized methods.

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8. DATA MANAGEMENT

8.1   Clinical Centers

EDIC data are collected at the Clinical Centers in accordance with established study procedures and submitted either directly to the DCC via direct data entry, or to the Central Units for evaluation and interpretation prior to being sent to the DCC (e.g. blood and urine samples, fundus photographs, OCT, ECGs). The DCC will send results of centrally evaluated research findings back to the Clinical Centers to be provided to the participant.

Study research data do not include the participant's personal identifying or contact information. Participants and their research data are identified by a unique study identification number that cannot be used to identify any individual subject. Personal identifying information is maintained only at the local Clinical Centers. All participant files at each of the Clinical Centers are kept in locked cabinets in locked offices.

Individual research results will not be communicated to the participant until those results have been analyzed and reported by the EDIC central units unless local observations during data collection suggest a safety issue for the participant. In this circumstance, local EDIC staff are expected to act expeditiously to protect participant safety and well-being. In addition, if in the process of data collection, a participant asks EDIC staff about the results, the staff member may respond based on his/her clinical knowledge and should remind the participant that all data collected is sent to a central expert reading center for analysis and interpretation, and that formal results will be transmitted back to the EDIC Clinical Center and participant after the formal analysis is complete.

A report summarizing the participants test results will be prepared by the DCC and made available to the EDIC Clinical Center to be provided to the participant, and if requested, to his or her health care provider(s). In general, data that have clinical relevance will be made available to participants. The decision to share research results that have little or no direct clinical relevance will be made by the EDIC Executive Committee. Individual DNA results will not be made available to individual participants, unless a compelling safety reason for doing so exists.

8.2   Central Units

Data are transmitted on a regular schedule via secure FTP to the DCC from the Central Units and the original reports stored on local file servers. Data from the Central Units is merged with the EDIC master database nightly.

8.3   Data Coordinating Center

The DCC is responsible for the collection and management of all clinical and laboratory data. The EDIC study uses a proprietary web-based data management system developed at the George Washington University Biostatistics Center, called MIDAS (Multi-modal Integrated Data Acquisition System). Data is entered by the Clinical Centers via a secure website and are transferred automatically to a database management system on the DCC's enterprise server. The data acquisition component provides interactive development of data dictionaries, form layout and formatting, real time editing including range and value checking, missing value reporting, skip patterns, etc.

Data management procedures during EDIC will remain focused on the goal of assuring the highest possible data quality while maintaining reasonable turnaround time and supporting ongoing analysis for monitoring and publication.

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The EDIC study also maintains two websites. The secure internal study website, allows for easier access to forms, protocols, policies, publications, participant reports, and overall communication with the Clinical Centers. The public website contains general study-related information and procedures for potential external collaborations.

8.4   Confidentiality

The Data and Clinical Coordinating Centers are responsible for ensuring participant confidentiality. Data submitted to the DCC and Central Units are masked regarding participant identity using the unique numeric identifier with the participant's initials that was assigned at the beginning of the DCCT. Biosamples and data that are transferred to the NIDDK Repository will be further de-identified by the DCC prior to transfer.

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9. STATISTICAL METHODS

All statistical analyses, unless noted otherwise, will be based upon the total cohort of patients randomized into the trial. Although data on some patients may be missing at points in time, all relevant data available from each patient will be employed in all analyses. In this manner, biases due to subset selection will be minimized (50).

Careful consideration will be given to the significance levels to be employed in the various analyses. Where appropriate, an adjustment for the effects of multiple tests of significance will be employed to guarantee that the true type I error does not exceed the desired level for a specific set of related analyses, such as the Holm or Hochberg procedures (51). Where feasible, the closed testing procedure (52-53) will be employed that may provide greater power than the Holm or Hochberg procedures. In cases where exploratory analyses are performed, results that are nominally significant at the 0.05 level (two-sided) will be reported.

In the remainder of this section, more detailed descriptions are provided of statistical methods which could be applied to specific types of observations to assess the study objectives.

9.1 Prevalence Analyses (Binary Outcomes)

Examples of such a binary outcome include the presence or absence of end stage renal disease at EDIC year 25 (2018). Such analyses of a binary variable typically describe the *prevalence* of an outcome at a specific point in time. Logistic regression models (50) will be employed to examine the effects of covariates on the odds of the binary outcome at that time (the odds ratio) and to assess the homogeneity of a covariate effect through tests of interaction. In these models likelihood ratio tests of effects will be employed and the strength of the effect measured by a partial entropy R^2 for each covariate (50). Value-added plots (54) will be employed to explore whether transformations or polynomial covariate effects are warranted rather than a simple linear effect. Goodness of fit will be assessed by the Hosmer-Lemeshow test and over-dispersion using the tolerance limits on the ratio of the Pearson Chi-square to its df (50). If the model assumptions are violated, the robust estimate of the covariance matrix of the estimates will be employed as the basis for confidence intervals and tests of significance (50).

Generalized estimating equations (55) with a logit link will be employed to assess the effects of covariates on the odds of an outcome over repeated points in time, allowing for the correlation among the repeated measures. Partial Wald or score tests will be used to test covariate effects and Madalla's R^2 (50) used to describe the strength of effect for each covariate.

9.2 Cumulative Incidence (Life-Table) Analyses

A principal set of outcome analyses will consist of survival (life-table) analyses of time-to-event outcomes.

9.2.1 Continuous Time Observations. Event times are obtained in continuous time when the day or date of an event is known, and the date at which the subject was last at risk (the right censoring time) is known. Examples are the times of death or myocardial infarction, etc. Analyses of such data will be performed using the standard Kaplan-Meier estimate of the survival or cumulative incidence function. The unadjusted log-rank test will be used to test for differences between groups, such as between the original DCCT intensive versus conventional groups (50,56-57). Analyses would be conducted to compare the two treatment groups adjusting for baseline characteristics if there are concerns for confounding or imbalances, or to improve power. The proportional hazards regression model (56,58-59) would be employed to

adjust for a set of covariates, or to jointly assess the influence of a set of factors simultaneously. In exploratory analyses, the assumption of proportionality will be tested using the test of Lin (60) and using other graphical methods (61). If non-proportionality is found, then either an alternate model may be employed, such as the proportional odds model (62-63) or transformations of the covariates may be employed, or time effects may be included in the model. Alternately, since the coefficient estimate under non-proportional hazards still converges to a finite constant, this could be interpreted as an average log hazard ratio and the precision (SE) and significance assessed by the robust covariance estimate of Lin and Wei (64).

9.2.2   Grouped Time. In many instances, however, the exact time of an event is not known, such as when CKD3 (eGFR <60 ml/min) is first observed from a serum creatinine value at an annual visit and we only know that the "event" may have occurred any time between the current and last evaluation. For outcomes observed with a fixed schedule over time, since all subjects have the same schedule of assessments (e.g. eGFR annually), a fairly standard simple procedure has been employed. Basically, for an analysis of annual renal assessments during the DCCT, the time to a renal event (e.g., CKD3) employed in the analysis is the scheduled time of the evaluation in whole years (1, 2,...) rather than the exact study day or fractional year of the visit. Patients who remain event-free will have a right censored time (period of observation) as of the day last evaluated. Since the outcome can only be observed when an examination is conducted, this leads to the construction of a modified Kaplan-Meier survival (or cumulative incidence) function (50). In a proportional hazards analysis, the discrete logistic model of Cox (58) will be employed. These are the basic analysis strategies employed for such analyses in the DCCT and EDIC. With frequent monitoring, Lachin (65) shows that this discrete time analysis provides nearly the same level of power as would an analysis where the actual event is observed in continuous time.

Poisson regression models (50,66) may also be applied to such discrete interval data (67-68). These models have the advantage of modeling the absolute risk rather than the relative risk as is the case for the proportional hazards model. This model also readily admits use of time-dependent covariates. These models require that one either assume that the background hazard is constant over time or that it can be modeled by covariate effects in the model. The proportional hazards model, however, conditions on the variation in the background hazard function so that it is not explicitly estimated as part of the model. In previous analyses of the effects of glycemic exposure on the risk of progression of microvascular complications in the DCCT, both Poisson and proportional hazards models were employed, both yielding similar results for the estimates of the principal covariate effects.

During EDIC, different subsets of patients had different schedules of examinations, such as renal measurements in one-half the cohort and lipids in the other half one year, and the opposite the next year. In this case the analysis will be stratified by whether the subject was randomized in an odd or even year.

9.2.3   Interval Censored Observations. However, the simple grouped time methods above would not apply to the analysis of retinopathy because only a quarter of the subjects had an evaluation in any given year except during EDIC years 4 and 10 during which all subjects were evaluated. Such data are *interval censored* because only the interval of time in which an even occurred is known, and the intervals may differ among patients. For interval-censored event time data, methods are also available that take into account the exact day of each successive visit and the length of the exact interval in days between successive visits. For example, EDIC (2015) presents such analyses of further progression of retinopathy over 18

years of EDIC that included all evaluations in all patients. Turnbull (69) described an estimator of the survival distribution (event-free distribution) for such interval-censored data and Finkelstein (70) described a generalization of the proportional hazards regression model to such data. However, both procedures require the estimation of a large number of nuisance parameters to describe the underlying background survival distribution. Younes and Lachin (63) described a family of regression models which provide a regression spline estimate of the background hazard (and thus cumulative incidence) functions and which include the proportional hazards and proportional odds models as special cases. Therefore, this procedure also provides a generalization of the log-rank test to such data. See also Pan (71), Boruvka and Cook (72) and Wang et al. (73).

These methods are non-parametric in that no form of the underlying hazard function is assumed. However, they involve various nuisance parameters that must also be estimated to fit the model. Another approach is to employ a parametric model with a specific underlying hazard function with only one extra shape parameter, such as an accelerated failure time model using the SAS PROC LIFEREG to describe covariate effects on the time acceleration factor (56). Such models, however, are not directly interpretable in terms of the covariate effects on the underlying hazard or survival functions. Rather, a parametric model, such as the Weibull model of Odell, Anderson and D'Agostino (74) could be employed that yields an estimate of the covariate effects on the relative risk of the event over time, in the same manner as the expression of covariate effects in the Cox PH model. The model can be fit using a Weibull accelerated failure time model from which the Weibull model parameter estimates and covariance matrix can be obtained (50). This approach was used in the prior DCCT/EDIC papers on retinopathy (17,75-77). Weibull model analyses that employ fixed and/or time-dependent covariates can also be obtained from the models of Sparling, et al. (78). This model was used to assess time-dependent covariate effects on the risk of retinopathy progression over EDIC (77).

9.2.4   Competing Risks. The risk of some events will be curtailed due to competing risks, such as the analysis of the incidence of laser therapy for retinopathy where some subjects die before such an event occurs. In this case, the deaths are not simply right-censored. Nevertheless, a Cox PH model analysis of the event time with right censoring on death still has a valid interpretation as the effect of the model covariates on the cause-specific hazard function for the event (79).

A more precise analysis would be to describe a true estimate of the cumulative incidence of the index event (e.g. laser therapy for retinopathy) adjusting for the incidence of the competing risk (mortality), such as an estimate of the sub-distribution function for the index event (80-82). Fine and Gray (83) also provide an extension of the Cox PH model to the analysis of covariate effects on the cumulative incidence function itself that accounts for covariate effects on both the cause specific hazard function for both the index and competing risk events. These approaches are especially useful when there are differences between groups in the incidence of mortality itself which must be considered in addition to the differences in the incidence of the outcome (e.g. laser therapy).

The methods for competing risks extend in a similar fashion to applications in which a study subject can move among a number of $k>1$ states over the course of the study, called multistate models (56,84-85).

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9.3　Incidence of Recurrent Events

In some cases, a subject may experience the same or like events over time, such as recurrent hospitalizations. Most such recurrent event outcomes will be observed in calendar (continuous) time. For such data, Andersen et al. (86) describe methods for the estimation of the underlying incidence rate function over time and develop a generalization of the logrank and other tests of significance of differences between groups with respect to the incidence function over time (50). The incidence rate (intensity) function estimates can be smoothed using a kernel-smoothed estimator as described by Ramlau-Hansen (87-88). To account for the effects of covariates on the incidence rate, either the Poisson regression model (50,66) or the multiplicative intensity model (50,57,84,89) will be employed. The multiplicative intensity model is a generalization of the proportional hazards model which allows for recurrent events in the same subject over time. However, it does so using a rather unrealistic assumption that the successive event times are conditionally independent of those that preceded. This assumption was relaxed in the proportional rate model of Lin et al. (90) that also employs the robust information sandwich estimate of the covariance matrix of the coefficient estimates. These models can also be employed to assess the association between outcomes and a time-dependent covariate. These methods were employed for the assessment of the association between glycemic exposure and the risk of hypoglycemia in the DCCT (19) and a forthcoming update over EDIC.

9.4　Rates of Events

In other cases, however, such as episodes of hypoglycemia during EDIC, the exact dates of recurrent events are not known. Rather, only the number of such events over an interval of time is reported. The incidence of such events will be summarized as a crude rate. Such rates will be presented as the number of events per 100 patient-years based on the ratio of the observed number of events to the total patient-years of exposure. The standard error for such rates will be computed allowing for "over-dispersion," i.e. assuming that the EDIC subjects have some underlying distribution of intensities (hazards) rather than the usual restrictive assumption that the same intensity applies to all subjects (50). The risk ratio (relative risk) will be used to summarize the difference between groups, and tests will be based on the large sample estimate of the variance of the log relative risk.

Poisson regression models will be employed to assess covariate effects on the rate of such events (50), expressed as a risk ratio (relative risk), and robust methods for inference will be employed if the model Poisson assumptions are violated (50). If a preliminary test of the homoscedastic Poisson assumption is significant, then either a zeros inflated Poisson model or alternate parametric models such as a negative binomial model will be employed (50). With longitudinal observations, we will consider models allowing the underlying baseline intensity to change with time using nonparametric tests (91) and mixed or marginal Poisson models (92-93).

9.5　Ordinal Outcomes

An ordinal outcome is a nominal assessment with multiple (>2) categories with an implied ordering, such as no nephropathy, microalbuminuria only, albuminuria only, or end-stage renal disease at a point in time. Simple proportions in each category will be used to describe the prevalence within each category at a given point in time, and differences between groups tested using the 1 df Mantel-Haenszel test of mean scores (94), or using the Wilcoxon signed rank test with the adjustment for tied ranks (95). A proportional odds model (94) will be used to examine covariate effects on the prevalence within each ordered category. If the test of the proportional odds assumption is rejected, then that implies the need to model covariate effects on each category separately. In this case, the odds of each category versus a designated reference category (e.g. no nephropathy) at a specific point in time will be assessed using a multinomial

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logit model (94). In essence, this model simultaneously fits a logistic model for C-1 comparisons of each positive category versus the reference category. The results of these models will be summarized as above for a logistic regression model. For a longitudinal analysis of covariate effects on repeated ordinal assessments over time, a proportional odds model with GEE will be employed (96). Alternately, the difference between groups in the longitudinal ordinal assessments can be tested using the Wei and Lachin (97) multivariate rank test.

9.6   Analyses of Quantitative Data

For quantitative (numerical) variables with no point of truncation, e.g. the albumin excretion rate (AER) in mg/24 h, simple differences between groups will be assessed by a Wilcoxon test (95). Models adjusting for covariate effects will be conducted using normal errors regression models (98). Partial residual or value-added plots will be employed to determine whether a transformation or a polynomial best represents a covariate effect rather than a simple linear term. The homoscedastic normal errors assumptions will be tested using the Shapiro-Wilks test of normality of residuals and White's test of homoscedasticity of error variances (99). If violations are detected, then an appropriate transformation will be sought. If still violated, all inferences will be based on White's robust estimate of the covariances of the estimates (99) that provides consistent estimates of the variances of the coefficient estimates.

9.7   Marginal Repeated Measures Analyses

Many assessments are repeated at intervals during the DCCT and EDIC for which repeated measures analyses will be conducted. Most such analyses will employ multivariate methods for the analysis of repeated quantitative, ordinal or qualitative measures.

The normal errors mixed model will be employed for an analysis of covariate effects on repeated quantitative measures over time using an "unstructured" covariance matrix for the repeated measures (55,100). Such "marginal" analyses provide an assessment of covariate effects on the average of values over time, or at specific points in time when covariate by time effects are employed. For example, these models will be used to evaluate the interaction between group and time to determine if previous intensive care was associated with persistent changes in eGFR levels over time.

For variables that do not satisfy the normal errors assumption, or those that are ordinal or nominal in nature, alternate methods may be employed. These include the multivariate non-parametric Mann-Whitney rank analysis for quantitative or ordinal measures (91,97,101) and the multivariate analysis of qualitative observations (102). These methods are intrinsically marginal in that the treatment group difference is assessed at each point in time, and an overall assessment is derived by pooling the results over time. In the simplest case of a binary outcome variable, e.g. ESRD present or absent, the marginal analysis consists of the comparison of the simple prevalences (proportions present) at each visit, which are then used to compute a risk difference (or relative risk or odds ratio) at each visit, which are averaged over all visits.

These methods have been used in the analyses of the prevalence of various outcomes over time in EDIC. In these analyses, a variety of multivariate tests of significance can be used (101). A commonly used test is based on the minimum variance efficient weighted average of the summary measures of treatment group differences over time (Mann-Whitney differences, odds ratios, etc.), termed the test of aggregate association. This test, analogous to the Mantel-Haenszel test, is appropriate when a common value of the summary measure is assumed to exist. Alternately, the Wei-Lachin test of stochastic ordering is more general in that it tests the hypothesis of no difference over time against the alternative hypothesis that the summary measures for all visits tend to differ in the same direction over time, such as where the outcome values tend to be systematically higher

(or lower) in one group than the other. This test is based on the unweighted simple average of the summary measures and has been shown to be a maximum efficient robust test against the family of alternatives where the groups differ in the same direction over time, but not to the same degree (103). Because the latter test is directed towards more general differences, it has been preferred by the investigators in the analyses of the DCCT/EDIC results. Lachin (104) also shows that this simple test also provides an efficient method for the assessment of treatment group differences in a set of multiple outcomes.

To evaluate the effects of covariates, including time-dependent covariates, on quantitative or qualitative outcomes over time, regression models based on the method of generalized estimating equations (55,105-107) will also be employed. This method can be used to estimate a common covariate effect for all visits over time, or visit specific effects can be estimated which can then be used in a test of stochastic ordering if desired.

9.8   Random Effects "Growth Curve" Models
For many EDIC outcomes, the longitudinal rate of change of the outcome over time will be analyzed based on the within-subject "slopes" of the regression of the outcome on time. These are commonly known as growth curve analyses. These analyses are especially common in the analysis of measures of renal function and were extensively employed in the analyses of the rate of change in AER over time.

A general family of such models has been described by Laird and Ware (108) and Jennrich and Schluchter (109), among many others. Laird and Ware (108) referred to the simplest form of these models as the "two-stage" random effects model. These models assume a common "shape" to the regression of the outcome over time for each subject (e.g. linear, quadratic, log-linear, etc.) with a corresponding within-subject component of variance, and then assume that the regression parameters in the population of subjects have some overall distribution with an average curve over time (e.g. mean intercept and slope) and between-subjects variance components. Usually, this "mixing" distribution is assumed to be multivariate normal. Given the assumed shape of these curves and the assumed mixing distribution, estimates of the average parameters (mean intercept and slope) and the within- and between-subjects variance components are obtained.

These models can incorporate the effects of subject-specific and time-specific covariates. Therefore, such models can be used to describe the average pattern of change in the outcome over time and to assess the effects of various covariates on the average values at any point in time, or on the pattern of change over time (110).

These mixed models (100) are essentially parametric in that they assume that the within-subject residuals are normally distributed and that patient-slopes in the population are also normally distributed. For some measures in the DCCT, these assumptions may not apply. In these cases, it will be necessary to explore a transformation of the data, such as the log transformation, which improves the distributional assumptions of the model. For some measures, such as microalbuminuria, a log transformation may be more biologically meaningful. When the rate of change in an individual subject is described on the log scale, it is implied that the percentage change over time is a constant for each subject rather than the absolute magnitude of the change being a constant for each subject, as is implied by a linear slope in the original measurements.

9.9   Informatively Censored and Missing Observations
All of the above methods assume that missing values are missing at random (111), and (efficient) unbiased results can be obtained using the direct likelihood method or EM algorithm

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(112), multiple imputations (113-114) and inverse probability weighting (115). This assumption, however, may not be appropriate in some instances.

For point prevalence analyses, other informative mechanisms in addition to mortality may apply, such as where patients who develop congestive heart failure are unable to attend the clinic visit for other EDIC outcome assessments. These instances are more problematic because some assumptions are then required regarding the nature of the association between the reason for missing data (termed "missingship") and the values of the missing observations. In the case where it can be assumed that patients who have informatively missing values have "worse" values than any observed non-missing values, then a rank analysis can be performed with a worst rank score assigned to the informatively missing observations (116). For example, patients who have died are usually assumed to have a worse quality of life than that of those who survive and complete a quality of life questionnaire.

For longitudinal growth curve analyses, various methods have been proposed (117-121). Some of these methods estimate the relationship between the repeated measures within subjects and the likelihood of informative censoring, which is then used to obtain a less biased estimate of the overall mean curve parameters (intercept and slope). Another approach which has been shown to be unbiased, but not as efficient under weaker assumptions, is to simply use an unweighted average of the within-patient coefficients (120).

9.10   Numerical Outcomes with Truncation

Some numerical measures are truncated, such as a coronary artery calcification score that is immeasurably small and reported as "zero", or a nerve conduction velocity where no response is elicited. In such cases, it is inappropriate to treat the truncated values as missing, and also inappropriate to treat the values as zero. Analyses of such measures at specific points in time can be conducted using a "worst rank" analysis (116). In such an analysis, all values below the limit of truncation are assigned a rank that is less than that of all observed values. A rank analysis is then conducted using the Wilcoxon rank test. For the analysis of multiple or repeated measures, the Wei-Lachin multivariate rank test can be employed (101) and the Mann-Whitney statistic can be used to describe the magnitude of group differences in the distribution of the outcome. A stratified analysis can also be conducted to adjust for covariate effects.

A TOBIT regression model (122) will be used to assess covariate effects on such truncated measures obtained at a specific point in time. This method simultaneously assesses a covariate effect on the probability of having a measurable value (above the limit of truncation) and the quantity of the measurement. This method has been used to assess group differences and covariate values on the propensity to have measurable calcification of the coronary arteries, where a substantial number of study subjects had unmeasurably small levels of calcification (if any).

9.11   Mediation Analyses

Mediators (e.g., HbA1c) are variables in the causal pathway between the exposure (e.g., DCCT treatment group) and the outcome (e.g., mortality), and they are useful in explaining the mechanisms by which the exposure affects the outcome. Under Baron and Kenny's mediation paradigm (123), three regression models are employed:
1. regressing the outcome on the exposure;
2. regressing the mediator on the exposure; and
3. regressing the outcome on both the exposure and the mediator.

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A change in the estimate of the exposure effect from model 1 to model 3 is evidence of mediation. More specifically, the total effect of the exposure on the outcome (Exposure → Outcome path) in model 1 can be decomposed in the direct effect (Exposure → Outcome path) in model 3 and the indirect effect (Exposure → Mediator → Outcome path) in model 3. Furthermore, the mediation proportion, defined as the proportion of the total effect explained by a particular mediator (i.e., the indirect effect divided by the total effect), will also be reported.

With time-to-event data (e.g., time to death), the proportional hazards (PH) assumption is not preserved under marginalization (i.e., the PH assumption cannot hold for both models 1 and 3) (124). Instead, the Aalen additive hazards model will be used for the time-to-event outcome (i.e., models 1 and 3) (59). When properly adjusted for confounders, the results of these mediation analyses also have causal interpretation (125-127).

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