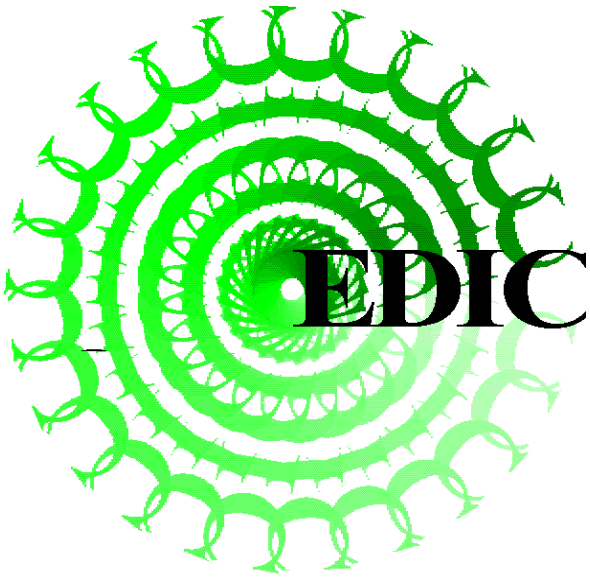

REQUEST FOR COLLABORATION(S)
FOR THE
DCCT/EDIC STUDY

Diabetes Control and Complications Trial /
Epidemiology of Diabetes Interventions and Complications Study

Date: January 21, 2019

https://edic.bsc.gwu.edu

Letter of Intent Due: February 21, 2019 (optional)
Proposal Due: March 15, 2019

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REQUEST FOR COLLABORATION (RFC)
DCCT/EDIC STUDY

1. INTRODUCTION

The **Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study** Research Group is seeking investigators to propose ancillary studies to be performed with the DCCT/EDIC study. The current RFC is designed for investigators who wish to work with the DCCT/EDIC Research Group, including the DCCT/EDIC Coordinating Centers located at the George Washington University Biostatistics Center (Data Coordinating Center) and Case Western Reserve University (Clinical Coordinating Center), to perform ancillary research projects using the DCCT/EDIC stored data and biologic samples as well as proposals to perform new evaluations on the cohort.

The purpose of this announcement is to encourage applicants with the interest, scientific expertise, and experience to apply to the DCCT/EDIC Research Group to collaborate and propose ancillary studies to the core DCCT/EDIC study, described below. New proposals will need to be financially self-sustaining. Specifically, all of the costs associated with a new ancillary study will need to be supported by budgets from the collaborating investigators. In the past, the funding for such ancillary studies has been provided through new NIH (e.g. R01) funding, foundation funding as well as other funding mechanisms.

2. DCCT/EDIC SUMMARY

The Diabetes Control and Complications Trial (DCCT, 1983-1993) established the importance of intensive diabetes therapy, aimed at achieving glycemic control as close to the non-diabetic range as safely possible, in preventing and decreasing the development of long-term microvascular complications (1). The observational follow-up Epidemiology of Diabetes Interventions and Complications Study (EDIC, 1994-present) has confirmed persistent benefits on more advanced microvascular and peripheral neuropathic complications (2-7). EDIC has established a durable salutary effect of past metabolic control on future complications in the setting of the dissipation of the metabolic differences between the two original DCCT treatment groups over time (“metabolic memory”) (2,8). EDIC has also demonstrated a benefit of intensive metabolic control on atherosclerosis, cardiovascular complications and mortality which is largely mediated by glycemia (9-13). Numerous other complications of diabetes have been investigated and the dominant relationship with glycemic control has been established (14-17). Other factors including genetics risk factors, biochemical markers, and surrogate measures of microvascular and cardiovascular disease have also been extensively investigated.

Of the original cohort (n=1441), approximately 1200 participants, representing 92% of the surviving cohort, continue to be actively followed over the 35 years since recruitment began. The DCCT/EDIC cohort is the most carefully phenotyped and genotyped population of people with type 1 diabetes studied over the majority of their diabetes history. DCCT/EDIC has published more than 300 papers describing its scientific contributions (https://edic.bsc.gwu.edu/web/edic/publications). A summary of the scientific advances provided by DCCT/EDIC during its first 30 years can be found in the following summary papers (18,19).

3. ANCILLARY STUDIES

The core DCCT/EDIC study has expanded its scientific and clinical contributions by engaging investigators from both within and outside of the DCCT/EDIC Research Group to perform "ancillary studies". Such studies take advantage of the data already collected in DCCT/EDIC to perform new analyses of collected data including phenotypic data, genetic analyses, biosamples, imaging, other clinical and scientific information, and other biometry, and to perform new measurements on the cohort. Considering the limited access to our cohort, usually in a single annual visit, and the substantial burden that is already placed on participants and local clinical center staff, such new measurements need to be carefully considered and organized.

Numerous ancillary studies (some utilizing only a portion of the cohort) have been conducted over the years. They have focused on: novel cardiovascular risk factors, cardiac imaging, skeletal health, epigenetics, cognitive function and decline including neuroimaging, physical dysfunction, urologic and sexual function complications, advanced glycation end products, and numerous other topics.

Of note, all previous ancillary studies have required full financial support independent of the core study, including coverage of any costs incurred by the clinical centers (e.g. additional participant transportation cost and clinical center staff time), the Data Coordinating Center (e.g. for statistical support or other administrative support), or by any other study laboratory or central unit. Funding for such studies has been provided by independent R01s, other federal funding, foundations, and other sources. Similarly, all proposals for new ancillary studies will be required to be self-supporting.

4. DESCRIPTION OF DCCT/EDIC RESOURCES AND SAVED SAMPLES

The DCCT/EDIC participants are extremely well-characterized with numerous biomedical measurements performed over time and stored biosamples, genetic material and other data relevant to the investigation of the causes of morbidity and mortality in diabetes. Serial assessments of microvascular complications in the eye and kidneys, and peripheral and autonomic neuropathy have all been performed longitudinally with state-of-the-art measurements from DCCT baseline. Quality-of-life measures and other assessments necessary for health economic analyses have also been performed. Comprehensive cognitive test batteries have been performed at DCCT baseline, end of DCCT, and again at EDIC year 12, thus providing serial assessments over an approximately 20-year time frame. Vascular measures of carotid intima media thickening at EDIC years 1, 6 and 12, cardiac vessel calcification using CT at EDIC year 8, and cardiac MRI at EDIC year 12 are all available. Conventional CVD risk factors including blood pressure and lipid levels, and numerous other innovative CVD risk factors are available. Moreover, information on genotypes of special interest to studies of a variety of complications and glycemia is available.

A complete listing of the data collected during DCCT/EDIC and the available biosamples are listed in **Appendix A**. This Appendix also includes a listing of past ancillary studies, separately for those involving additional observations from participants and those based only on stored biosamples and/or existing study data.

Potential collaborators should note that substantial DCCT/EDIC biosamples and past study data are available from the NIDDK Repositories. Investigators should consider using the repository as the first mechanism for obtaining access to DCCT/EDIC phenotypic information and biosamples. The repository is open to requests for materials at any time and such requests

should not involve the DCCT/EDIC research group unless additional materials (specimens, data, etc.) from the DCCT/EDIC research group are required.

With this announcement, the DCCT/EDIC research group is seeking new ancillary study proposals that cannot be conducted using repository materials alone.

Finally, owing to past studies many specimens in the DCCT/EDIC stores, and those of the NIDDK Repositories, have been depleted. Applicants should contact the NIDDK repository and/or the Data Coordinating Center (address below) to assess the feasibility of any study that would make use of these stored specimens.

5. PROCESS FOR PROPOSAL SUBMISSIONS AND REVIEW TIMELINE

The goal of the application process outlined in this RFC is to coordinate requests to the DCCT/EDIC Research Group so that applications will be submitted and considered on a regular annual schedule. A single submission date will facilitate the coordinated review of requests so that the relative merit and burden can be comprehensively assessed and coordinated to avoid excessive burden on the participants, the clinical centers, Coordinating Centers, and other central labs/reading centers.

1) **February 21, 2019: Letter of Intent (optional)**

Organizations or individuals intending to submit a proposal in response to this announcement are requested to inform The George Washington University Biostatistics Center of their intent by writing a letter providing the organization name, Principal Investigator, address, phone and email. A Letter of Intent (LOI) is requested to assist in the review process but is not required in order to submit an application. Institutional signature(s) are not required on LOI.

Letters should be addressed and emailed to:

Barbara Braffett, Ph.D.
The George Washington University Biostatistics Center
6110 Executive Blvd, Suite 750
Rockville, MD 20852.
braffett@bsc.gwu.edu

2) **March 15, 2019: Ancillary Study Application (Appendix B)**

A completed ancillary study application is submitted for review by the DCCT/EDIC Research Review Committee. Any questions regarding the completion of the application, including inquiries regarding the appropriateness of proposed projects for DCCT/EDIC, whether similar or overlapping projects have been performed or are underway and any other questions should be addressed to Barbara Braffett, Ph.D. at the DCCT/EDIC Data Coordinating Center (braffett@bsc.gwu.edu). Final applications should be submitted to Dr. Braffett at the address above.

3) **April-May, 2019: Research Review Committee and Executive Committee review**

4) **June, 2019: Final review and approval by DCCT/EDIC Research Group**

5) **October, 2019: Earliest submission date for NIH grants**

In future years this announcement will be reissued so that each year investigators will have the opportunity to submit a new ancillary study proposal.

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APPENDIX A: Past, Current, and Future DCCT/EDIC Measurements and Frequency of Measurements

Measurement	Frequency of Measurement		
Medical History & Physical Examination	**DCCT 1983-1993**	**EDIC 1994-2016**	**EDIC 2017-2022**
Updated health history	Quarterly during DCCT	Annually	Annually
Current medications	Did not collect	Annually	Annually
Height, weight, BMI	Baseline; quarterly	Annually	Annually
Waist circumference	Did not collect	Annually	Annually
Ankle:brachial index by Doppler	-----	Annually thru 2012; ½ cohort annually	Once in 2019-2020
Smoking, drinking	Baseline; annually	Annually	Annually
Exercise and activity	Baseline; annually	Annually	Annually
Blood pressure, pulse	Baseline; quarterly	Annually	Annually
Insulin dose and delivery	Baseline; quarterly	Annually	Annually
Electrocardiogram	-----	Annually	Annually
Self-reported hypoglycemia	Baseline; quarterly	Annually: events in 3-month period prior to visit	Annually: events in 3-month period prior to visit
Laboratory Measures			
HbA1c	Baseline; quarterly	Annually	Annually
Fasting lipids	Baseline; annually	½ cohort annually	½ cohort annually
Urine albumin and creatinine	Baseline; annually	½ cohort annually	½ cohort annually
Serum creatinine	Baseline; annually	Annually	Annually
hs-Troponin	-----	-----	Annually
N-terminal pro b-type natriuretic peptide	-----	-----	Annually
Microvascular Outcomes			
OCT, Ultrawide	-----	-----	Once in 2018-2020
Fundus photography	Baseline; every 6 mos	¼ cohort annually; full cohort EY 4, 10	Once in 2018-2020
Visual acuity, intraocular pressure	Baseline; every 6 mos	¼ cohort annually; full cohort EY 4, 10	Once in 2018-2020
National Eye Institute Visual Function-25	-----	¼ cohort annually; full cohort EY 4, 10	Once in 2018-2020
Estimated GFR	Baseline; annually	Annually	Annually
AER	Baseline; annually	½ cohort annually	½ cohort annually
Confirmed clinical neuropathy	Baseline; 5 yrs, close	EY 13/14	Will not collect
Cardiac Autonomic Neuropathy	Baseline; every 2 yrs	EY 13/14, 16/17	Will not collect
MNSI, 10-gram filament examination	-----	Annually	Annually
Adjudicated Events			
Cardiovascular disease	As it occurs	Annually	Annually
Dialysis or kidney transplant	As it occurs	Annually	Annually
Death	As it occurs	As it occurs	As it occurs
Questionnaires			
Health Care Delivery	-----	Annually	Annually
Diabetes Quality of Life	Annually	Odd EDIC years	Odd EDIC years
36-item Short Form Health Survey (SF-36)	Closeout	Odd EDIC years	Odd EDIC years
Quality of Well-Being (QWB-SA)	-----	EY 13/14	EY 24/25
EuroQOL (EQ-5D)	-----	EY 17	EY 24/25
Urologic Complications	-----	Annually since EY 2010	Annually

Aging Batteries and Assessments			
Cognition			
DCCT/EDIC Neuropsychological Subset	Baseline; 2, 5, 7 yrs, closeout	EY 12	EY 24/25, 27/28
Montreal Cognitive Assessment (MoCA)	-----	-----	EY 24/25, 27/28
NIH Toolbox Subset	-----	-----	EY 24/25, 27/28
Cognitive Change Index (CCI-SR)	-----	-----	EY 24/25, 27/28
Symptom Check List 90 (SCL-90R)	Annually	EY 10, 17, 18/19	EY 24/25, 27/28
Patient Health Questionnaire-9 (PHQ-9)	-----	-----	EY 24/25, 27/28
Physical Functioning			
Short Physical Performance Battery (SPPB)	-----	-----	EY 24/25
Goniometry measure of shoulder flexion	-----	EY 18/19	EY 24/25
Grip strength	-----	-----	EY 24/25
Reaction time	-----	-----	EY 24/25
Disability of Arm, Shoulder, Hand (DASH)	-----	-----	EY 24/25
NHANES Physical Function & Disability	-----	-----	EY 24/25
International Physical Activity (IIPAQ-SF)	-----	-----	EY 24/25
Current Ancillary Studies			
Hypoglycemia-Arrhythmia			EY 24/25
CGM sensor			EY 24/25
ECG heart rate monitor			EY 24/25
Fitbit			EY 24/25
Blood glucose meter			EY 24/25
Daily Logbook			EY 24/25
Skeletal Health			EY 24/25
DXA Scan			EY 24/25
HR-pQCT (6 clinics only)			EY 24/25
Block Food Frequency (BFFQ)			EY 24/25
Neuroimaging			EY 25/26

Ancillary Studies that Involve Participants

Study/Project Name and Description	Collection
DCCT Family Study – Study of familial clustering and correlation of severity of eye & kidney disease in first degree relatives of the DCCT proband.	1992
Lipoproteins – Study of the natural history of changes in lipoprotein distribution and LDL composition to predict atherosclerosis and premature death.	1993
Mechanisms of Vascular Disease – Study to determine why individuals living with diabetes have an increased incidence of heart and blood vessel disease.	1993
Carotid Ultrasound – Study of the effects of diabetes on carotid arteries (intimal thickening) in large blood vessels.	1994, 1998, 2004
Coronary Calcium – Study of the effects of diabetes and atherosclerosis in the coronary arteries and large blood vessels.	2000
Genetic Family – Study of first degree relatives to determine the associated genes for the development of diabetes and its complications.	2001
UroEDIC I – Study to determine the prevalence and severity of bladder dysfunction and sexual dysfunction in T1DM.	2003
Neurocognitive – Study of the effects of diabetes control in T1DM on learning skills, memory, problem-solving, and mental efficiency.	2004
Neurology – Study of the effects of diabetes control in T1DM on nerve damage to both the peripheral and autonomic nervous systems.	2006, 2009
Cardiac MRI – Study to evaluate the heart and its blood vessels for problems related to both structure and function in T1DM.	2007
Fundus Comparison Methods – Comparison / validation study employing both standard film and digital images.	2007
Skin Autoflourescence – Study to evaluate the use of a non-fluorescence device to assess the risk of diabetes-related complications.	2009
URO EDIC II – Study to examine the relationships between diabetes and bladder and sexual health and to assess the differences in PSA/testosterone in males.	2010
C-peptide Pilot – Study to determine the likelihood of measurable amounts of stimulated C-peptide in selected subjects (n=60).	2011
Epigenetics – Study to determine if “metabolic memory” is related to expression/repression of certain genes in the development of eye/kidney complications	2011
Cheiroarthropathy – Study to determine the prevalence of cheiroarthropathy, identify risk factors, and determine associations with other diabetes complications.	2012
ReproEDIC – Study to measure serial biochemical markers of ovarian reserve and to examine the association between these markers and diabetes-related risk factors.	2013
Gastric Emptying– Study to determine the rate of gastric emptying in selected subjects (n=80).	2013
Dermal AGEs – Study to assess the association between urine AGEs and the risk of retinopathy, nephropathy and neuropathy in T1DM.	2013
Hearing Impairment– Study to determine whether hearing impairment occurs in T1DM more frequently than in non-diabetic controls, and to identify risk factors.	2013
C-peptide – Study to determine the likelihood of measurable amounts of stimulated C-peptide in the full cohort.	2016

Hypoglycemia-Arrhythmia – Study to determine the effects of hypoglycemia on the risk of ventricular and other arrhythmias.	2017
Skeletal Health – Study to examine the variability of bone microarchitecture associated with diabetes-related factors.	2018
Neuroimaging – Study to examine how T1DM affects neuro-cognitive impairments using magnetic resonance imaging techniques and cognitive testing.	2018

Ancillary Studies that Involve Stored Biologic Specimens / Data

Study/Project Name and Description	**Collection**
Biomarkers of Vascular Disease – Study to evaluate the effect of selected biomarkers in predicting the development of micro- and macro-vascular complications.	2008
CVD Biomarkers – Study to investigate molecular mechanisms of oxidant stress in T1DM.	2009
Vitamin D – Study to evaluate the associations of circulating vitamin D metabolites with risk of incident microalbuminuria, impaired glomerular filtration rate, and hypertension in T1DM.	2010
Haptoglobin – Study to assess the association of Hp 2-2 with incident CAD in T1DM.	2012
Glycated Albumin – Study to determine if glycated albumin contributes to the risk relationship between glycemia measured by A1C and risk of retinopathy, nephropathy	2012
Oxidative Biomarkers – Study to assess the relationship between oxidative and advanced glycation end products and the risk of retinopathy, nephropathy and CVD.	2013
Expanded Epigenetics – Study to evaluate the role of epigenetic DNA methylation in T1DM complications and metabolic memory.	2015
AGE – Study to correlate urine and plasma AGE's with retinopathy, nephropathy, and neuropathy.	2017
Leukocyte Endothelial Adhesion – Study to evaluate LEA as a quantitative cellular endophenotype biomarker for diabetic retinopathy.	2017

APPENDIX B: Ancillary Study Application Process

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.

A preliminary description of the project should be submitted to the EDIC Data Coordinating Center (DCC). The **3 page** summary should include the following information:

1. Investigators and collaborators name, role, and institutional affiliation. Attach NIH biosketches for investigators and key personnel.
2. Planned start and end dates.
3. Estimated costs and plans for funding, including the anticipated source of funding.
4. Design and methods:
    - Hypotheses to be tested with statement of primary and secondary goals and objectives.
    - Brief background, significance, and rationale.
    - Justification for performing study within DCCT/EDIC.
    - Description of additional methods, procedures, or tests to be carried out on study participants, including:
        - Any ophthalmologic, renal, cardiovascular, neurologic, psychological, or other evaluation to be performed, as well as tests on biological samples.
        - Any substances to be injected or otherwise administered to the participants.
        - Any observations to be made or procedures to be conducted on participants outside of the clinic.
        - Any extra clinic visits required of the participant or any prolongation of the participant's usual annual, one-day clinic visit.
        - Any additional specimens (blood, urine, etc.) to be obtained or additional procedures to be done on specimens collected according to the EDIC Protocol.
        - Any additional questionnaires or surveys to be administered to the participants.
    - Data needed (a) from the EDIC study central database and (b) from additional tests, surveys, etc. Note that data and/or samples should be requested from the NIDDK data and/or bio-repository if available to meet the needs of the proposed study.
    - Analysis plan.
    - Sample size and justification, including power calculation.
    - Burden on participants and impact on the EDIC study clinical centers and central units.
    - Measures to be taken to ensure participant safety and confidentiality.

The applicant should explicitly state that they understand and commit to adhere to the DCCT/EDIC Publications and Presentations Policies https://edic.bsc.gwu.edu/web/edic/publications.

In addition to the 3-page proposal, each collaborating investigator should provide a statement that they have reviewed and approved the application, are committed to participate and that they approve the funding arrangements and level of funding proposed.

All proposals will be forwarded for review to the Research Review Committee and Executive Committee, and if approved, also by the DCCT/EDIC Research Group.

If the ancillary studies proposal is approved and investigators subsequently prepare a grant proposal for funding, the grant must be sent to the Data Coordinating Center with adequate time for review (at least 4 weeks prior to submission). If support is required from 1) the DCC or its subcontractors including the Central Biochemistry Laboratory and the central reading units or 2) the Clinical Coordinating Center (CCC) for study coordinator effort and clinical center protocol-based needs, the requirements (staffing and work scope) should be discussed with the DCC and CCC at least 5 weeks prior to the application due date. Final budget components and documentation should be completed by the applicant at least 15 days before the submission due date.