National Institute of Diabetes and Digestive and Kidney Diseases

Evaluating Neurocognitive Complications of Pediatric Type 1 Diabetes (T1D) and Potential Risk and Protective Factors

RFA-DK-23-009 and RFA-DK-23-010

Pre-Application Webinar

July 17, 2023

1:00 – 2:00 pm EDT

Funding provided by
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Webinar Reminders

- Please use the **chat feature** to post any questions.
- We will provide an overview of the RFAs, with questions answered during the **Q & A** session at the end of the webinar.
- **Slides** from today's webinar and **FAQs** will be posted to the pre-application webinar website in the upcoming weeks.

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Agenda

- Background and objectives of the RFAs
- Application information
  - Biostatistics Research Center NOFO (RFA-DK-23-009)
  - Clinical Center NOFO (RFA-DK-23-010)
- Frequently asked questions (FAQs)
- Q & A from participant chat

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Background: Neurocognition in T1D

- Adults with type 1 diabetes (T1D) diagnosed in childhood are at increased risk for neurocognitive complications.
- Early age of onset of T1D and duration of disease increase the risk for impaired neurocognitive function.
- Research **earlier in the developmental spectrum** and with **contemporary cohorts** can inform mechanisms of neurocognitive complications associated with T1D, critical periods for prevention and intervention, and strategies to mitigate neurocognitive complications later in life.

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Background: Neuroimaging Findings

- Based on structural and functional neuroimaging, children with early onset T1D may be at higher risk for brain abnormalities relative to children without diabetes.

- Due to conflicting results and underpowered cohorts, the complex structure-function dynamics are not well understood.

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Background: Potential Risk & Protective Factors

Current research points to **potential risk and protective factors** associated with neurocognitive functioning, including but not limited to:

- Hyperglycemia
- Hypoglycemia
- Glucose time-in-range
- Glycemic variability
- Diabetic ketoacidosis (DKA)
- Clinical severity at the time of diagnosis
- Use of automated diabetes management systems
- Internalizing symptoms (e.g. depressive symptoms, anxiety)
- Externalizing symptoms
- Social determinants of health (SDoH)

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Current Funding Opportunities: U01 Clinical Trial Not Allowed

- RFA-DK-23-009 - Evaluating Neurocognitive Complications of Pediatric Type 1 Diabetes (T1D) and Potential Risk and Protective Factors – Biostatistics Research Center (U01 Clinical Trial Not Allowed)
- RFA-DK-23-010 - Evaluating Neurocognitive Complications of Pediatric Type 1 Diabetes (T1D) and Potential Risk and Protective Factors – Clinical Centers (U01 Clinical Trial Not Allowed)

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Scientific Staff

Applicants are strongly encouraged to reach out to NIDDK staff with any questions, prior to submission!

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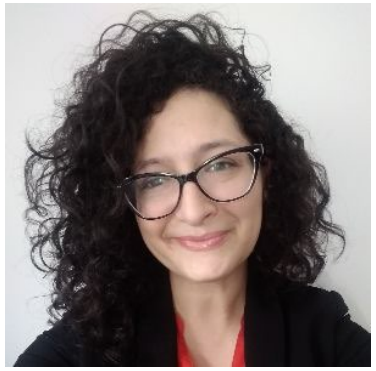

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U01 Mechanism

- The U01 mechanism is a cooperative agreement, in which NIH is a partner in the research project.
- As such, NIDDK will have substantive scientific involvement in the proposed project.
- **Please review** the Cooperative Agreement Terms and Conditions of Award listed in the NOFOs.

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Objectives

The **overarching goals** are to establish a diverse longitudinal cohort of pediatric patients newly diagnosed with T1D that will allow investigators to:

1. Better understand the impact of T1D on the developing brain, including neurocognitive and psychosocial functioning

2. Identify and evaluate potential risk and protective factors associated with T1D-related neurocognitive impact, including magnitude and duration of blood glucose time in range (TIR), time spent in hypoglycemia or hyperglycemia and other continuous glucose monitoring (CGM) metrics, and diabetic ketoacidosis (DKA) status at diagnosis

3. Assess potential associations between use of newer and emerging diabetes management technologies (e.g. automated diabetes management systems) and neurocognitive functioning among children with T1D

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NOFO Considerations

Structure

- One **Biostatistics Research Center (BRC)** will be selected to lead study execution, sample/data management, and analyses (RFA-DK-23-009).
- Up to 10 **Clinical Centers (CCs)** will be selected to join the clinical consortium as performance sites and support data collection and analyses (RFA-DK-23-010).
- PIs from the BRC and Clinical Centers, along with the NIDDK Project Scientist, and community engagement representative will form a **Steering Committee.**
- The **Steering Committee** will develop and execute a common protocol to meet the study objectives.
- **Total project period:** 5 years, with the first year dedicated to establishing the study protocol to be executed across all Clinical Centers, as well as site-specific start-up activities (hiring, etc.).

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Steering Committee Responsibilities

- Develop policies and procedures for the study group and ensure the policies are implemented
- Meet regularly (including at least one annual in-person meeting) to develop the core study protocol and review study progress
- Identify opportunities for ancillary study policies to expand the scientific output of the group

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BRC Responsibilities

- The BRC will provide the organizational framework for the management, direction, and overall coordination of the national multi-site consortium, including but not limited to:
  - Study performance
  - Dissemination of plans and policies across CCs
  - Oversight of data collection, along with management and analyses of clinical and laboratory data
  - Data harmonization and integration

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CC Responsibilities

- Each CC will collaborate with the BRC and other CC investigators to design and implement the uniform study protocol. This includes:
  - Recruitment of the study population at the CC site
  - Collecting data in accordance with established study procedures
  - Submitting samples and data to the BRC for management and integration

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NOFO Considerations

Research Strategy

- BRC applications should include:
  - Significance of the proposed study
  - Plans for standardization, quality assurance, and monitored adherence to the core study protocol and data collection across clinical sites
  - Formation and management of necessary study cores
  - Primary outcome for the study and estimated sample size
  - Statistical methods to analyze the types of data that may be collected
- CC applications should include:
  - Significance of the proposed study
  - Study team's experience
  - Preliminary data addressing feasibility of the proposed study
  - Detailed description for the study design
  - Sample size calculation

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NOFO Considerations

Sample

- Pre-pubertal children newly diagnosed with T1D
- Must reflect the racial, ethnic, and socioeconomic diversity of the US and youth with T1D at the consortium level, with each site focused on recruiting a diverse participant population
- Must include an appropriate comparator population of youth without type 1 diabetes

Sample Domains to Assess

- Clinical characteristics
- Neurocognitive/behavioral/biopsychosocial
- Brain structure and function
- Social determinants of health

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Use of Common Data Elements (CDEs)

- Investigators are encouraged to review NIH Common Data Elements (CDEs) to ensure that selected measures may be applicable across studies and facilitate the establishment of common data elements
- Resources include:
  - PhenX SDOH Assessments Collection
  - NIH CDE repository
  - Existing NIH-funded ongoing cohort studies

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Multidisciplinary Teams

- The research team should include complementary and requisite knowledge, skills, and experience to conduct the core protocol, including but not limited to:
  - type 1 diabetes
  - neurocognitive development
  - human neuroimaging
  - automated diabetes management systems

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Community Collaborators

- Applicants are expected to:
  - Use community engaged approaches in designing a protocol for the application
  - Describe the process to facilitate meaningful, sustainable collaboration with persons with diabetes, caregivers, clinicians, healthcare systems, community organizations, advocacy groups, and other relevant collaborators throughout the research process
  - Community collaborators will be key members of the steering committee

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Stakeholder Engagement Plan

- A Stakeholder Engagement Plan must be included with all applications to RFA-DK-23-010 (Clinical Centers).
- Meaningful stakeholder engagement entails active and relevant involvement of patients, caregivers, family members, clinicians, healthcare systems, advocacy groups, and other relevant stakeholders in the development, design, and execution of the study.
- It is expected that applicants will propose appropriate community engagement during the planned U01 period and how these activities will be used.

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Budget

- Application budgets need to reflect the actual needs of the proposed project
- **Biostatistics Research Center Budget:**
  - May not exceed $1.2 million in direct costs for grant year 1 (planning year) and $2.2 million in direct costs for each grant year 2 - 5
- **Clinical Center Budget:**
  - May not exceed $200,000 in direct costs for grant year 1 (planning year) and $400,000 in direct costs for each grant year 2 - 5

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Biostatistics Research Center Budget

- **Year 1 (Planning Year)**
  - PI/Co-I effort
  - Establishment of necessary study cores and contracts
  - Equipment and licenses
  - Training for site coordinators and key personnel at CCs
  - Coordination of consortium meetings (e.g. Steering Committee, Observational Study Monitoring Board (OSMB), stakeholder engagement activities)
  - Single IRB/regulatory approval
- **Years 2–5 (Protocol Implementation)**
  - PI/Co-I effort
  - Coordination of consortium meetings
  - Oversight of protocol execution (including scanner harmonization and ongoing trainings)
  - Central laboratory fees and applicable ongoing assessment licenses/fees
  - Processing and interpretation of neuroimaging results
  - Procurement of necessary clinical supplies (e.g. standardized glucose monitoring devices)
  - Data management and sharing
  - Single IRB services

Clinical Center Budget

- **Year 1 (Planning Year)**
  - PI/Co-I effort
  - Consortium-related meeting travel
  - Local travel for community engagement
  - Local community collaborator engagement activities
  - Initial hiring of staff

Applicants may assume that the cost of supplies related to cognitive and neuropsychological evaluation, CGM, and laboratory assays will be covered by the BRC budget

- **Years 2–5 (Protocol Implementation)**
  - PI/Co-I and staff effort
  - Costs associated with local conduct of study:
    - Neuroimaging assessment (not analysis/interpretation)
    - Consortium-related meeting travel
    - Participant reimbursement
    - Recruitment activities
    - Operating costs / Facility fees

Review Process

- Applications will be evaluated for scientific and technical merit by an appropriate Scientific Review Group convened by NIDDK.
- Determination of scientific merit will include standard and RFA-specific review criteria.
- All applications will receive a written critique.

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Review Criteria Specific to RFA-DK-23-009: *Biostatistical Research Center*

BRC Review Criteria	
Investigator(s)	How appropriate is the experience of the PD(s)/PI(s) and study team in managing a multi-site clinical consortium?
	How appropriate is the experience of the PD(s)/PI(s) and study team in aspects of scanner harmonization and standardization of imaging protocols across multiple imaging centers?
	To what extent has the study team demonstrated their proficiency in the management and integration of multi-modal datasets, to include cognitive/neuropsychological, neuroimaging, and clinical outcomes?
Approach	Are planned analyses and statistical approaches appropriate for the proposed study design?
	Are the plans to standardize, assure quality of, and monitor adherence to the study protocol and collection of data appropriate?
	Is there a plan to complete data analyses within the proposed period of the award?
Protection of Human Subjects	How well does the Data Safety Monitoring Plan describe patient safety issues relate to the specific assessments described in the proposed study?

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Review Criteria Specific to RFA-DK-23-010: *Clinical Centers*

CC Review Criteria	
Investigator(s)	How appropriate is the experience of the PD(s)/PI(s) and study team in conducting neurocognitive studies with children?
	How experienced is the study team in conducting neuroimaging assessments at their proposed site(s)?
	How experienced are the PD(s)/PI(s) and the study team with diabetes technologies including CGM and automated diabetes management systems?
Approach	To what extent does the application incorporate validated assessments related to social determinants of health?
Environment	How well does the supporting evidence document the ability of the individual site or center to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; and (4) operate within the proposed organizational structure?
Protection of Human Subjects	How well does the Data Safety Monitoring Plan describe patient safety issues related to the specific assessments described in the proposed study?

Non-responsive applications

- Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review and responsiveness by NIDDK, NIH. Applications that are incomplete, non-compliant and/or nonresponsive will not be reviewed.
- Applications proposing any of the following will be considered non-responsive and withdrawn:
  - Animal or in vitro studies
  - Foreign components/non-US entities
  - Clinical interventions

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Submitting your Application

- Letter of Intent (*optional*): September 26, 2023
- Application Due Date: **October 26, 2023**
  - By 5:00 PM local time of applicant organization
- Scientific Merit Review: March, 2024
- Advisory Council Review: May, 2024
- Earliest Start Date: July, 2024

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Application Submission Contacts

- Scientific/Research Contacts
  - Maureen Monaghan Center, PhD (NIH/NIDDK): maureen.center@nih.gov or 301-402-3269
  - Theresa Teslovich Woo, PhD (NIH/NIDDK): theresa.woo@nih.gov or 301-480-1871
- Peer Review Contact
  - Michele L. Barnard, PhD (NIH/NIDDK): michele.barnard@nih.gov or 301-594-8898
- Financial/Grants Management Contact
  - Christina Coriz (NIH/NIDDK): corizc@niddk.nih.gov or 301-594-8848

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Application Submission Contacts

- Technical Support
  - eRA Service Desk: https://era.nih.gov/need-help or 301-402-7469/866-504-9552
  - General Grants Information: grantsinfo@nih.gov or 301-637-3015
  - Grants.gov Customer Support: support@grants.gov or 800-518-4726

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Thank you joining us!

Slides from today's webinar and FAQs will be posted to the pre-application webinar website in the upcoming weeks.

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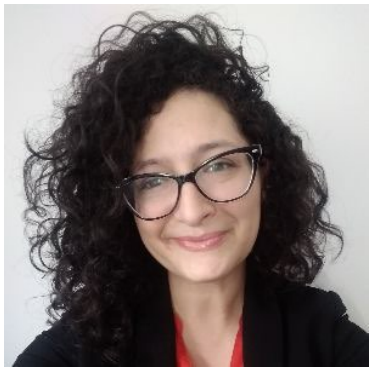

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