Protocol

Title: Continuous Glucose Monitoring in Patients With End-Stage Kidney Disease and Burnt-Out Diabetes

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PROTOCOL TITLE: Continuous Glucose Monitoring in Patients with End-Stage Kidney Disease and Burnt-Out Diabetes

Short Title: Burnt-Out Diabetes

Discovery Project:

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1. Study Summary

Project Title	Continuous Glucose Monitoring in Patients with End-Stage Kidney Disease and Burnt-Out Diabetes
Project Design	Observational cross-sectional study.
Primary Objective	• To determine if utilizing Continuous Glucose Monitor (CGM) devices is superior to HbA1c for assessing glycemic control in patients with end-stage kidney disease on dialysis.
Secondary Objective(s)	• Compare daily mean glucose values between patients with burnt-out diabetes and non-diabetic subjects with ESKD.
Research Intervention(s)/Interactions	• Continuous glucose monitoring (CGM) compared to glycemic metrics including CGM and HbA1c.
Study Population	Individual with and without diabetes on hemodialysis and with HbA1c < 6.5% on no diabetes therapy will be eligible to enroll.
Sample Size	40 patients. 20 patients with burnt-out diabetes and 20 non-diabetic subjects with ESKD
Study Duration for individual participants	10 days
Study Specific Abbreviations/ Definitions	POC, Bedside point-of-care; CGM, Continuous glucose monitoring; T2D, Type 2 diabetes; BG, blood glucose; OAD, Oral antidiabetic; MARD, mean absolute relative difference; CBG, capillary blood glucose
Funding Source (if any)	N/A

2. Objectives

Diabetes is the number one cause of end stage kidney disease (ESKD) and need for dialysis. It is estimated that diabetes affects up to 40% of patients with ESKD[3]. Glycosylated hemoglobin (HbA1c) is the gold standard to assess glycemic control in patients with diabetes and indicates the average glycemia during the past 2-3 months. In subjects with ESKD; however, the accuracy of HbA1c is reduced because of anemia, shortened erythrocyte lifespan, erythropoietin therapy, among others factors. To overcome the limitations of HbA1c, continuous glucose monitoring (CGM) technology has been shown to provide a comprehensive glycemic control in patients with diabetes and may overcome the limitations of these methods in the ESKD population; however, the accuracy of CGM in ESKD has not been established.

About one fourth of patients with diabetes on dialysis therapy experience resolution of their hyperglycemia, as defined by an HbA1c less than 6.5%, without antidiabetic therapy. This

phenomenon is known as “burnt-out diabetes”. Because HbA1c may be falsely low in ESKD, we will use CGM to assess glycemic control and confirm whether patients with burnt-out diabetes have normoglycemia or not. We hypothesize that the use of CGM may represent a better tool to assess glycemic control than HbA1c in patients with ESKD on dialysis. To prove this hypothesis, we will compare glycemic metrics including CGM and HbA1c, in 20 patients with burnt-out diabetes and in 20 non-diabetic subjects with ESKD.

II. Specific Aims:

Study Aim. Compare glycemic metrics including CGM and HbA1c in patients with burnt-out diabetes and in non-diabetic subjects with ESKD.

Hypotheses:

1. The use of CGM represents a better tool to assess glycemic control than traditional markers (HbA1c) in patients with ESKD and renal replacement therapy (dialysis). Patients with burnt-out diabetes will show higher mean daily glucose values and higher time-above range (TAR > 180 mg/dl) compared to non-diabetic subjects with ESKD.

3. Background

Diabetes and chronic kidney disease. More than 37 million adults, or 14.7% of all Americans aged 18 and older, are living with diabetes. Controlling hyperglycemia is foundational to diabetes management and is necessary to reduce the risks of chronic diabetes complications and death. Diabetic nephropathy accounts for great morbidity, as diabetes is the number one cause of chronic kidney disease (CKD) and end stage kidney disease (ESKD) in the US[2]. It is estimated that diabetes affects up to 40% of patients with ESKD[3].

Assessment of glucose control in patients with advanced CKD/ESKD is complex due to changes in glucose homeostasis, potential effects on assays of glycemia, and altered pharmacokinetics of diabetes medications[2]. Glycosylated hemoglobin (HbA1c) has been the gold standard to assess glycemic control in patients with diabetes. HbA1c reflects the average glycemic value over approximately 3 months. Although HbA1c is associated with chronic complications of diabetes in patients with normal kidney function, its predictive value is uncertain in patients with increased red cell turnover (hemolysis) and in subjects with ESKD or eGFR <30 ml/min. HbA1c reliability in ESKD is reduced because of anemia, shortened erythrocyte lifespan, protein-energy wasting, and malnutrition-inflammation cachexia syndrome, among others[4,5].

To overcome the limitations of HbA1c, alternative methods to assess long-term glycemic control have been proposed including fructosamine and glycated albumin[2]. Fructosamine measures ketoamines formed by non-enzymatic glycation of serum proteins. It is a useful index for glycemic control over the prior 2 to 4 weeks, and some studies have reported that fructosamine more accurately reflects blood glucose control than HbA1c in anemic patients with ESKD on dialysis. However, there may be falsely low readings in the presence of hypoalbuminemia due to protein-energy wasting and in peritoneal dialysis due to dialysate

protein loss. Glycated albumin is a useful marker reflecting glycemic control over the prior 2 to 4 weeks. In patients with ESKD, glycated albumin more rapidly reflects the status of blood glucose control than HbA1c. Like frucotsamine, there is potential for falsely low readings in patients with peritoneal dialysis with dialysate protein losses and hypoalbuminemia[2,5-8].

Continuous glucose monitoring (CGM) technology in the outpatient setting has transformed glucose monitoring for diabetes self-management, providing more comprehensive glycemic control data than intermittent point-of-care capillary blood glucose monitoring and HbA1c. Although the accuracy of CGM in ESKD has not been established, a recent prospective study in hospitalized patients with type 1 and type 2 diabetes reported good accuracy of CGM in patients with CKD[9].

Burnt-out diabetes. Once progressed to ESKD, up to one fourth of patients experience resolution of their hyperglycemia, as defined by an HbA1c level of less than 6.5%, and consequently are no longer on antidiabetic agents and insulin. This phenomenon is known as "burnt-out diabetes" which is likely due to various underlying factors, including but not limited to, malnutrition, reduced clearance and degradation of insulin, decreased kidney gluconeogenesis, and accumulation of uremic toxins[10]. These patients are likely at a greater risk of morbidity and mortality and an increased risk of hypoglycemic episodes[4]. There is a need for further research in patients with ESKD to establish what is the most appropriate tool to assess glycemic control in those with 'burnt-out diabetes'.

Our study will use CGM to measure patients' glucose with real-time levels as opposed to relying on surrogate markers like A1c. These results can give insight into the reality of glycemic control in these patients and can impact the best monitoring and treatment for patients with burnt-out diabetes. It is not known if patients with burnt-out diabetes have complete normoglycemia or if they may have episodes of (untreated) hyperglycemia, which may be associated with poor outcome. Accordingly, we will compare glycemic control by CGM in patients with burnt-out diabetes and non-diabetic patients with ESKD.

4. Study Endpoints

Primary safety and efficacy endpoints:

1) Frequency of overall and nocturnal hypoglycemia (< 70 mg/dl) by Dexcom G6 CGM (safety endpoint) [52].
2) Glycemic control, as measured by mean daily glucose concentration between groups by Dexcom G6 CGM (efficacy endpoint).

5. Study Intervention/Investigational Agent

The proposed CGM to be used in this study is the Dexcom G6, a factory-calibrated CGM system, that is innovative in many aspects: 1) it does not require finger stick glucose testing for calibration, 2) the sensor is small, compact, light-weight, 3) has no interference with several substance and drugs, and 4) effective glucose measures every 5 minutes (288 glucose measures per day).

6. Procedures Involved

Visit 1: All consenting subjects, with and without diabetes, will have a blinded Dexcom G6 CGM placed for up to 10 days (study duration). Consent procedure will be conducted during/after their hemodialysis sessions after explaining all study procedures. After providing informed consent, patients will have a sensor inserted by the study team. Insertion of the CGM sensor will be performed per manufacturer instructions and following an aseptic technique. After insertion of the sensors, providers will ensure proper hemostasis is achieved. Sensors will be removed if prolonged bleeding or severe pain occurs. Patients will be educated on study procedures and sensor care. The participants will be instructed to wear the CGM with the display off for 10 days while continuing regular, routine dialysis sessions. They will be instructed that the device will be removed at a future dialysis session after 10 days of wear.

Patients will be consented- after explanation of the procedure- for withdrawing about 5 ml of blood prior to dialysis to measure glycated albumin as well as fructosamine to assess glycemic control in dialysis patients with and without diabetes.

Visit 2: The CGM sensor will be removed after 10 days, and data will be downloaded at this time. HbA1c will be collected from patient medical record. In addition, we will collect information on clinical characteristics (age, sex, duration of diabetes and ESKD, dialysis, history diabetes treatment, duration of burn-out period, time off diabetes medications, comorbidities (hypertension, coronary heart disease, heart failure, COPD).

Clinical trial materials will be labeled and should be handled and stored according to the respective hospital's regulatory requirements.

For the safety outcome (primary outcome), a "hypoglycemia episode" is defined as a glucose < 70 mg/dl, "clinically significant hypoglycemia" is defined as a glucose <54 mg/dl, and "severe hypoglycemia" is defined as a glucose < 40 mg/dl by POC testing or by CGM for > 15 minutes. An episode is not counted as being "new event" unless the sensor glucose is above 70 mg/dL or above 54 mg/dL at least once following an episode of hypoglycemia. A "hypoglycemic event rate" is defined as the number of hypoglycemic events per patient per day.

For the efficacy outcome, the "mean daily glucose concentration" is defined as the mean daily and fasting glucose concentration during the hospital stay up to first 10 days of therapy by POC testing and by CGM. A "nocturnal" hypoglycemia episode or a "nocturnal" clinically significant hypoglycemia episode is defined as an episode occurring during the time interval of 00:01 to 05:59.

7. Statistical Analysis Plan

Data Analysis. Data will be entered into REDCap to keep track of all results and to meet HIPAA and confidentiality regulations, provided by the Emory Research Information Technology Department. A p-value less than 0.05 will be considered significant. The data will be presented

as means ± SD. Statistical analysis will be performed using the SAS (version 9.2; SAS Institute, Cary, NC). All statistical analysis will be performed by Limin Peng, PhD, from Emory University.

Limin Peng, PhD, Professor of Statistics at the School of Public Health will assist with data analysis. We will measure outcomes such as average daily glucose, time in range between 70-140 mg/dl, time in range between 70-180 mg/dl, fasting, premeal, 2 hours post meal, and nocturnal (10 PM-6:00 AM) glucose values, time (%) in hyperglycemia (>180 mg/dL, >250 mg/dl). In addition, we will collect information on glycemic variability by CGM.

Sample Size. This study will be a pilot study, as there is no preliminary data available for this patient population utilizing the Dexcom G6 CGM. Currently, there are 850 patients undergoing Hemodialysis at Emory Dialysis Centers. Up to 40% of these cases should be due to diabetes mellitus, and anywhere from ~25-35% of these patients should meet the definition of burnt-out diabetes, resulting in ~100 patients who should qualify as participants. Currently, we have identified ~20 patients with burnt-out diabetes on hemodialysis.

8. Data and/or Specimen Banking

Data collection records with personal identifiers will be stored in locked file cabinets. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, research coordinators, and the IRB at Emory University.

9. Sharing of Results with Participants

Study results will be shared with the subjects at their request, including laboratory values, blood pressure measurements, and physical exam measurements.

10. Study Timelines

All consenting subjects, with and without diabetes, will have a Dexcom G6 CGM placed for up to 10 days (study duration). The CGM sensor will be removed after 10 days.

The anticipated time required to complete primary analysis of results is 6 -9 months

11. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Be at least 18 years old
2. Dialysis treatment for more than 3 months
3. HbA1c less than 6.5% at the first clinic visit
4. Willing to wear a CGM for 10 days

Exclusion criteria

1. Have used insulin or any diabetes treatment during the last 3 months
2. Be pregnant or plan to become pregnant during the study
3. Known allergy to medical-grade adhesives

4. Taking acetaminophen (more than 1 gram every six hours) or hydroxyurea (may interfere with sensor membrane)
5. Current or anticipated use of stress steroid doses (prednisone </= 5 mg or its equivalent is allowed)

Most participants will not be of child-bearing age. However, pregnancy may impact the accuracy of the CGM device. We will ask all women of their menopausal status. If a woman is of child-bearing age, we will administer a pregnancy test before enrolling in the trial.

12. Population

This study will be a pilot study, as there is no preliminary data available for this patient population utilizing the Dexcom G6 CGM. Patients qualify for the burnt-out diabetes group if they have 1. Been diagnosed with diabetes in the past, 2. Now have last A1c of <6.5%, and 3. Are no longer on any diabetic medications, and meet all other inclusion and exclusion criteria. Patients may qualify for the control group if they have never been diagnosed with diabetes in the past and meet all other inclusion and exclusion criteria.

Currently, there are 850 patients undergoing HD. ~40% of these cases should be due to diabetes mellitus, and anywhere from ~25-35% of these patients should meet the definition of burnt-out diabetes, resulting in ~100 patients who should qualify as participants. Currently, we have identified ~20 patients with burnt-out diabetes on hemodialysis.

13. Vulnerable Populations

This study does not involve a vulnerable population.

14. Local Number of Participants

A total of 40 subjects will be invited to participate from Emory dialysis centers.

15. Recruitment Methods

Recruitment will involve identification of hospitalized patients at Emory dialysis centers who meet the study eligibility criteria. Screening for eligibility will be performed from medical records prior to informed consent being signed. There will be no specific efforts to promote recruitment other than making hospital staff aware of the study. All eligible participants will be included without regard to sex, race, or ethnicity. Participation in this study is voluntary. Recruitment: The study team will perform pre-screening on subjects scheduled for their clinic visit and will approach potential candidates during the dialysis session. If potential candidate expresses interest and qualifies for study participation, full consent procedure will be conducted during/after their hemodialysis sessions. All consenting subjects, with and without diabetes, will have a Dexcom G6 CGM placed for up to 10 days (study duration).

16. Withdrawal of Participants

1. The subject may withdraw at will at any time.

2. The subject may be withdrawn from the trial at the discretion of the investigator because of a safety concern or if judged non-compliant with trial procedures or included in contravention to the inclusion and/or exclusion criteria.
3. Subject requiring hospital admission.
4. Pregnancy or intention to become pregnant.

Subject replacement. There will be no replacement of subjects in this trial.

17. Risk to Participants

1. Sensor Insertion: We will use a commercially available (FDA approved) glucose sensor Dexcom CGM. We will use an aseptic technique following manufacturer recommendations. After insertion of the sensors, providers will ensure proper hemostasis is achieved. Sensors will be removed if prolonged bleeding or severe pain occurs. It's uncommon but inserting the sensor could cause infection (<1%), bleeding or pain (~10%), and wearing the adhesive patch can irritate the skin (~10% on prior studies). We will avoid insertion over irritated or damage skin, exclude subjects who are sensitive to adhesive and use an aseptic technique to avoid this. The principal investigator and our study team is experienced in performing studies using CGM in high-risk population (hospitalized, acutely ill patients), with minimal risk involved.

2. Skin allergy to adhesive material may be developed in <5% of subjects. This will usually do not require treatment and goes away a few days later.

Sensors Contraindication: Sensors will be removed before MRI, CT, diathermy procedures, per manufacture instructions.

Sensor precautions: Avoid using sunscreen or insect repellents from having contact with sensor.

18. Potential Benefits to Participants

1. Participation in the study may determine the presence of hyperglycemia in subjects with so called burnout diabetes. If so, intervention with antidiabetic drugs may be indicated at the discretion of their treatment provider.

The study may help in the management of patients with diabetes on dialysis. In addition, the main goal of the intervention study is to prevent hypoglycemia.

19. Risk of anticipated benefit. Compensation to Participants

Participation in this study is voluntary. Subjects will receive twenty-five dollars ($25) after CGM removal on the second visits.

Information from medical records, interviews and tests that are part of this research will be collected.

20. Data Management and Confidentiality

Data collection

To assure each subject's confidentiality, data collected under this protocol will be coded and stored in a secure locked file cabinet with access limited to those directly related to the conduct of this study. Electronic versions of these data will be stored on a limited access, password protected, secure server with coded patient identifiers. Study participants will be assigned a code number that will be linked to their name. Only study personal will have access to the linked name-code key. Except for the informed consent form, data will be marked solely with the participant's code number.

Statistical analysis

The primary endpoint in this study is to compare glycemic metrics including CGM and HbA1c in patients with burnt-out diabetes and in non-diabetic subjects with ESKD. We will first compare clinical characteristics including demographics, duration of diabetes and dialysis between patients with and without DR using two-sample t-tests or nonparametric Wilcoxon tests. We will perform multivariate linear regression to evaluate the group difference while accounting other possible confounders (patient age, type of dialysis) for the primary outcome. The secondary endpoints include compare daily mean glucose values between patients with burnt-out diabetes and non-diabetic subjects with ESKD, most recent HbA1c, comorbidities (hypertension, cardiovascular disease, heart failure, peripheral neuropathy, autonomic/GI neuropathy, cerebrovascular disease, peripheral vascular disease, depression, anxiety, cognitive impairment/dementia), adherence and barriers to screening recommendations, we will analyze continuous secondary outcomes in the same way that we propose for the primary endpoint. A p-value less than 0.05 will be considered significant. The data will be presented as means ± SD. Statistical analysis will be performed using the SAS (version 9.2; SAS Institute, Cary, NC).

Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Principal investigator and other study personnel will not use data or PHI for any purpose other than conduction of the study. All PHI used will be de-identified and coded by the Principal investigator or designee. The code will be kept in a password protected computer file. PHI will be disclosed when required for audit by regulatory agency.

The personal information will be kept private and confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. The results of this study may be shown at meetings or published in journals to inform other doctors and health professionals. Subject identity will be kept private in any publication or presentation about the study. People and organizations that may inspect and/or copy research records to assure the quality of the data and to analyze the data include:

- Medical staff who are directly or indirectly involved in your care related to this research.
- People who oversee or evaluate research and care activities at Emory University.
- People from agencies and organizations that perform independent accreditation and oversight of research;
    - Emory offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research
    - Government agencies that regulate the research
    - Public health agencies
    - Research monitors and reviewer
    - Accreditation agencies

21. Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

The safety of interventions and treatments associated with this protocol will be under continuous review by the investigative team. As this study is unicentric and observational trial, it is felt that a formal Data Safety Monitoring Board is not necessary to insure the prompt implementation of patient safeguards.

Select one of the following (do not delete this table; review the guidance document for definitions):	
☐ Medium Complexity	
☐ High Complexity Category A	
☒ High Complexity Category B *If choosing this category for a study under an IND or IDE because you believe the study intervention does not significantly impact morbidity or mortality, please provide your rationale: : We will use a commercially available (FDA approved) glucose sensor Dexcom CGM. No major risks are expected with the use of the CGM device. Pain and bleeding with insertion is minimal.*	

Monitoring Table 3

DSMP Requirement	How this Requirement is Met	Frequency	Responsible Party(ies)
Real-time review of participant data during initial data collection.	Review on real-time by CRC every time information is obtain	*Expectation is that this happens every time you obtain information.*	CRC
100% review of regulatory files	Review at study initiation by CRC and when the requests	*Reviewed at a minimum of first and close-out visits*	CRC Principal Investigator
100% review of consent forms	Review at study initiation and every time a new patient is added to the study	When modifications apply.	CRC Principal Investigator
Review of credentials, training records, the delegation of responsibility logs (if applicable)	Review at study initiation per PI	*Reviewed at a minimum of first and close-out visits*	CRC Principal Investigator
Comparison of case report forms (CRF) to source documentation for accuracy and completion	Review first chart with the PI and once a month throughout study	*Reviewed at a minimum of first and close-out visits*	CRC Principal Investigator
Review of documentation of all adverse events	Review and report once the adverse effect is noted	At the time the AE been reported	CRC Principal Investigator
Monitoring of critical data points (eligibility, study endpoints, etc.)	Review when a new patient is added to the study	*Reviewed at a minimum of first and close-out visits*	CRC Principal Investigator
Laboratory review of processing and storage of specimens	N/A	*Reviewed at first and close-out visits and at least biannually*	N/A
Assessment of laboratory specimens stored locally	N/A -	N/A	N/A

Test article accountability review	Will keep inventory sheet throughout study	*Reviewed at first and close-out visits and at least biannually*	CRC Principal Investigator
Accountability logs, dispensing records, and other participant records	Will keep accountability log throughout study	*At least biannually*	CRC Principal Investigator
For FDA regulated studies, the following requirements apply:	N/A - not FDA study		
Monitoring methods (may include centralized, on-site, and self-assessment)	N/A - not FDA study		
*For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations.			

Subject safety:

Any AEs will be reported in the Emory REDCap computerized database, within 15 days of the event and any SAEs will be reported to the Emory IRB within 24-48 hours of the event. The standard Emory IRB reporting guidelines for AE and SAE reporting will also be followed. The investigators and staff will enter all AEs into the REDCap database, and evaluate the SAEs, in close coordination with the Emory IRB. The investigators and staff will track and summarize AE frequency, severity, and relatedness at a frequency appropriate to ensure subject safety.

A periodic (annual unless otherwise specified) report of AE with a frequency > 5% will be provided for this clinical trial 1-2 months prior to IRB annual review. The Emory IRB reporting guidelines for UP, AE and SAE reporting should also be followed. Risks include local infection, inflammation, lightheadedness, pain or discomfort, bleeding at the CGM insertion site, bruising, itching, scarring or skin discoloration, hematoma (also known as a black and blue mark) caused by the leakage of blood under the skin, CGM Sensor or needle breakage during insertion, wear or removal.

Sensors may fracture or be retained in situ on rare occasions. In these rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain participants should consult with the investigator or prescribing physician for the best course of action. If there is no portion of the broken sensor wire fragment

or retained sensor wire visible above the skin, attempts to remove it without medical guidance are not advised.

Pregnancy will be an exclusion criterion. Pregnancy test will be performed prior to study procedures and thereafter at investigator's discretion. Women of childbearing age will be considered pregnant as demonstrated by a positive βHCG PT (Pregnancy Test) to be performed during study visits (blood draw) per investigator discretion. Investigators will follow Emory IRB protocol for reporting.

22. Provisions to Protect the Privacy Interest of Participants

All participant data will be kept confidential and de-identified. Access to research will be limited to clinical investigators, research coordinators, and the IRB at Emory University. Clinical data will be stored in a secure web-based database that requires password access.

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Principal investigator and other study personnel will not use data or PHI for any purpose other than conduction of the study. All PHI used will be de-identified and coded by the Principal investigator or designee. The code will be kept in a password protected computer file. PHI will be disclosed when required for audit by regulatory agency.

The personal information will be kept private and confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. The results of this study may be shown at meetings or published in journals to inform other doctors and health professionals. Subject identity will be kept private in any publication or presentation about the study.

23. Economic Burden to Participants

No additional cost to subjects

24. Informed Consent

After identification of eligible subjects these individuals will be provided basic information regarding the study and, if interested, they will then be screened by research staff using the inclusion/exclusion criteria delineated elsewhere in this protocol. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have any questions, and research staff will answer these questions. The principal investigator will also be available to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided

to the participant and a copy will be placed in the file that is maintained for each participant in the study office.

Non-English-Speaking Participants

Adults who speak any of the following languages (English, Russian, Spanish and Arabic) will be approached for participation in the study.

Participants who are not yet adults (infants, children, teenagers)

No subjects under the age of 18 will be recruited in this study.

Cognitively Impaired Adults

No subjects with cognitively Impaired Adults will be recruited in this study.

Adults Unable to Consent

No subjects Adults Unable to Consent will be recruited in this study.

25. Setting

This study will be conduct at Emory dialysis centers. Screening for eligibility will be performed from electronic medical records.

26. Resources Available

Emory University and Grady Hospital have combined ~1300 patients with ESKD on hemodialysis. Emory University Dialysis Center is a comprehensive dialysis service with 5 clinics located across the health system to provide services to over 800 patients, including 51% of patients with diabetes, ~ 88% on hemodialysis. In addition, Grady Dialysis Unit provides care for over 500 patients/year with 50% of patients with diabetes. This large number of patients will facilitate the recruitment and will generate important clinical information. We have put together a team of endocrinologists, and statistician to support and guide the discovery student. Given the 12 month period and the cross-sectional study design, we expect to recruit the adequate number of subjects. We will also work with our colleagues in the Division for assistance in identifying patients for this study.

Dr. Umpierrez, a Professor of Medicine at Emory University, will serve as the principal investigator and student's lead mentor. With Dr. Umpierrez' oversight, student will learn about the use of CGM, and best practices in obtaining consent and recruitment of participants. In addition, the student will learn on data acquisition, use of REDCap research dataset, entering data, and help with data analysis. Limin Peng, PhD, Professor of Statistics at the School of Public Health will assist with data analysis. The student will present the results in regional and national scientific meetings.

27. Multi-Site Research When Emory is the Lead Site

N/A

28. References

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29. Protocol Checklist

Protocol Section	Added to the protocol?
External Collaborators- if applicable, add each external collaborator information and indicate whether that institution's IRB will review (or has already reviewed) that individual's engagement in human participants research activities)	☒ **Yes**
Funding Source*: Include the information for the funding entity for this study. Please explain if this study is covered by a sub-award or other pertinent information. Say "department" if you do not have any other funding.	☒ **Yes**
Objectives*: Describe the purpose, specific aims, or objectives and state the hypotheses to be tested	☒ **Yes**
Background*: Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data. Provide the scientific or scholarly background for, the rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge	☒ **Yes**
Study Endpoints*: Describe the primary and secondary study endpoints. Describe any primary or secondary safety endpoints.	☒ **Yes**
Study Intervention/Investigational Agent*: Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.	☒ **Yes**
Drug/Device Handling: If the research involves drugs or devices, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on participants and be used only by authorized investigators. If using a drug, explain if the control of the drug is managed by IDS (or VA/Grady/CHOA research pharmacies). If not, provide IDS exemption document. If a device, explain how the device is being stored and managed.	☒ **Yes**
If the drug is under an FDA REMS, plan to complete the REMS checklist found here, on the IRB website.	☒ **Yes**
If the drug is considered a controlled substance, make sure you have filled out this form.	☒ **Yes**
If applicable, identify the holder of the IND/IDE/Abbreviated IDE. An Emory investigator who holds an IND or IDE is considered to be a Sponsor-Investigator (S-I). If the study is under an S-I, review this section of our website for additional requirements.	☒ **Yes**
Procedures involved*: Describe and explain the study design and include a study schema. Describe all research procedures being performed and when they are performed, including procedures being performed to monitor participants for safety or minimize risks	☒ **Yes**
Procedures-Minimizing risk*: describe the procedures performed to lessen the probability or magnitude of risks.	☒ **Yes**
Procedures- Drug/Device Use: describe all drugs and devices used in the research and the purpose of their use and their regulatory approval status	☒ **Yes**

Procedures-Source Records*: describe source records that will be used to collect data about participants. Attach all surveys, scripts, and data collection forms to the submission.	☒ **Yes**
Procedures-Data collection*: describe what data will be collected during the study and how that data will be obtained	☒ **Yes**
Procedures- Long Term Follow Up*: once all research-related procedures are complete, what data will be collected during this period. If no data is collected after procedures are completed, please state in the submission.	☒ **Yes**
Data and Specimen Banking: describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens. Depending on the volume and nature of the collection, this may require a separate repository-specific IRB submission. The VA Data Repository SOP is required if the study is creating a data repository at the Atlanta VA. List the data to be stored or associated with each specimen. Describe the procedures to release data or specimens, including the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.	☒ **Yes**
Sharing of Results with Participants*: Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with participants or others (e.g., the participant's primary care physicians) and if so, describe how the results will be shared If applicable (e.g. for studies involving scans and/or panels of exploratory testing on specimens) Plan for managing the types of findings that might arise. This should include any secondary findings that are being sought actively, findings that might be anticipatable, and findings that might be un-anticipatable. Plan for recognizing, analyzing, and handling incidental findings and how incidental findings will be communicated to participants during the consent process. If the plan is not to disclose any findings, then this should be included. This plan might include the option for participants to opt-out of receiving incidental findings. Description of the research team's responsibilities following disclosure of a finding. This should detail educational information about the nature of the finding, how to seek care from a clinician or specialist, obtaining health insurance to secure treatment, and/or referral to a clinical specialist, if one is required. Reminder to include language in the consent form to let the participants know your plans for this – see Modular Language for Informed Consent Forms on IRB website)	☒ **Yes**
Study timelines*: describe the duration of an individual participant's participation in the study; anticipated time to enroll all study participants and the estimated date for the investigators to complete this study (complete primary analyses)	☒ **Yes**
Inclusion and Exclusion Criteria*: describe how individuals will be screened for eligibility and the criteria that define who will be included or excluded in your final study sample	☒ **Yes**
Population*: describe the study popualation and indicate specifically whether you will include or exclude each of the following special populations: • Adults unable to consent • Individuals who are not yet adults (infants, children, teenagers)	☒ **Yes**

• Pregnant women • Prisoners Note: you cannot exclude people with limited English proficiency unless you can demonstrate the scientific need for such exclusion. Community Participation: For studies aimed at addressing issues that affect a certain community or group: How, if at all, will this study involve people from the target community in the design of the study? Conduct of the study? How will the results of the research be shared with the participants and/or the target community/ies? **If studying Race or Ethnicity, have you defined these terms, and explained their proposed mechanism of action if these characteristics will be used in an explanatory model?**	
Research with pregnant women, fetuses, or neonates: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☒ **Yes**
Research with neonates of uncertain viability: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☒ **Yes**
Research involving prisoners: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☒ **Yes**
Research involving children: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☒ **Yes**
Research involving cognitively impaired adults: review this checklist to verify you have provided enough information to ensure the safety and well-being of this population.	☒ **Yes**
Research involving economically or educationally disadvantaged persons: describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects	☒ **Yes**
Local Number of Participants*: Indicate the total number of participants to be accrued locally. If applicable, distinguish between the number of participants who are expected to be enrolled and screened, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures.) Provide your projected enrolling goals, including the percentage of participants according to sex and race.	☒ **Yes**
Recruitment Methods*: Describe when, where, and how potential participants will be recruited. Describe the source of participants. Describe the methods that will be used to identify potential participants. Describe materials that will be used to recruit participants. Attach copies of these documents with the application. If including advertisements, attach the final copy of them. When advertisements are taped for broadcast*, attach the final* audio/videotape. You may submit the wording of the advertisement before taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/videotape. Describe the amount and timing of any payments to participants. Reimbursement for expenses/travel? If using contests or raffles as incentive, you must offer entry to all potential participants, not just those who enroll in the study/complete study-related procedures, per Georgia State Law.	☒ **Yes**

All research recruitment through social media needs to follow this guidance, which does not allow the use of personal social media accounts for some recruitment activities.	
Withdrawal of Participants*: Describe anticipated circumstances under which participants will be withdrawn from the research without their consent. Describe any procedures for orderly termination. Describe procedures that will be followed when participants withdraw from the research, including partial withdrawal from procedures with continued data collection.	☒ **Yes**
Risk to Participants*: List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related to the participant's participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks. If applicable, indicate which procedures may have risks to the participants that are currently unforeseeable. If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant. If applicable, describe risks to others who are not participants.	☒ **Yes**
Potential Benefits to Participants*: Describe the potential benefits that individual participants may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit. Do not include benefits to society or others.	☒ **Yes**
Compensation to Participants*: Describe if/how subjects will be compensated for participation in this study. Indicate what method compensation will be delivered (e.g. cash, gift card, school credit). Describe the amount and timing of any payments to participants. How much? What kind? Is tax information required? (if so, must be reflected in the informed consent form). Will payments be pro-rated if a participant withdraws early?	☒ **Yes**
Data Management and Confidentiality*: Describe the data analysis plan, including any statistical procedures or power analysis. Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission. Describe any procedures that will be used for the quality control of collected data.	☒ **Yes**
Describe how data or specimens will be handled study-wide*: What information will be included in that data or associated with the specimens? • Where and how data or specimens will be stored? • How long the data or specimens will be stored? • Who will have access to the data or specimens? • Who is responsible for receipt or transmission of the data or specimens? • How data or specimens will be transported?	☒ **Yes**
Data Monitoring and Participants Safety (if this study is more than minimal risk, this section is required):	☒ **Yes**

Ensure that you review our Data and Safety Monitoring plan guidance for specific details about this section, and examples of what the IRB will be requiring according to the level of risk. If a DSMB is needed, please describe the composition of the board (if not already detailed in the protocol). Review this guidance for more information. If the sponsor protocol does not contain all required information, please in this section. Describe the plan to periodically monitor the data at the site level according to risk level. Include the appropriate completed monitoring table, if applicable. Description of the plan for notifying the IRB of reportable events, whether the sponsor requires reporting above and beyond the Emory IRB reporting requirements, and if so, a description of the requirements and plan for meeting them. Please address the specific details below. If deemed not applicable, please provide rationale: Subject safety: • Specific subject safety parameters • Frequency of subject safety observations • Individual responsible for safety monitoring • Subject stopping rules – under what conditions will a subject be removed from study participation and who will make the decision? • Study stopping rules - under what conditions will the study be modified or stopped and who will make the decision? • Reporting mechanisms (i.e. Deviations, adverse events, UPs) Data Integrity: • Specific data elements to be reviewed • Frequency of monitoring data, points in time, or after a specific number of participants • Individual responsible for data monitoring Additional considerations for FDA regulated trials Depending on the procedures affecting risks to participants, the site monitoring plan should specify: • Categorization of activities done centrally and those on-site if applicable • Monitoring methods (may include centralized/remote, on-site, and self-monitoring) • Reference to any tools used (i.e. checklists) • Identification of events that may trigger changes • Identification of deviations or failures that would be critical to study integrity	
Provisions to Protect the Privacy Interests of Participants*: • Describe the steps that will be taken to protect participants' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or whom they provide personal information. • Describe what steps you will take to make the participants feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of	☒ **Yes**

intrusiveness a participant might experience in response to questions, examinations, and procedures. • Indicate how the research team is permitted to access any sources of information about the participants.	
Economic Burden to Participants*: Describe any costs that participants may be responsible for because of participation in the research.	☒ **Yes**
Consent Process*: Describe where the consent process will take place, any waiting period available between informing the prospective subject and obtaining the consent; and the process to ensure ongoing consent. Describe the role of the individuals listed in the application as being involved in the consent process; the time that will be devoted to the consent discussion; steps that will be taken to minimize the possibility of coercion or undue influence; and steps that will be taken to ensure the participants' understanding. **Note**: If you are planning to obtain consent via electronic signature, please review this document. Additional guidance on consent documentation and process can be found on our website, under the consent toolkit.	☒ **Yes**
Consent Process-Non-English-Speaking Participants*: Indicate what language(s) other than English are understood by prospective participants or representatives. If participants who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those participants will be in that language. Indicate the language that will be used by those obtaining consent. If you checked N/A, please provide reasoning of why subjects with limited English proficiency are excluded. **Note**: if you stated that subjects with LEP will be enrolled, you are approved for the use of the Emory IRB short forms. Please read the guidance about the use of short forms here.	☒ **Yes**
Consent Process-Children: After determining if the subject is a child per GA law (or if enrolled outside GA, per state/country law), please describe whether parental permission will be obtained from: • Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. • One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care. When assent of children is obtained describe whether and how it will be documented per Emory Policies and Procedures	☒ **Yes**
Consent Process-Cognitively Impaired Adults: describe the process to determine whether an individual is capable of consent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require children to sign assent documents.	☒ **Yes**

Consent Process-Adults Unable to Consent: List the individuals from whom permission will be obtained in the order of priority. (E.g., durable power of attorney for health care, a court-appointed guardian for health care decisions, spouse, and adult child.) For research conducted in the state, review "46 LEGALLY AUTHORIZED REPRESENTATIVES AND SURROGATE CONSENT" to be aware of which individuals in the state meet the definition of "legally authorized representative." For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. Describe the process for the assent of the participants. Indicate whether: • Assent will be required of all, some, or none of the participants. If some, indicated, which participants will be required to assent and which will not. • If assent will not be obtained from some or all participants, an explanation of why not. Describe whether the assent of the participants will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require participants to sign assent documents	☒ **Yes**
Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception) Review the Emory IRB waiver document to ensure you have provided sufficient information for the IRB to make these determinations. If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations.	☒ **Yes**
Setting*: Describe the sites or locations where your research team will conduct the research including where the subject will be identified and recruited, where the research procedures will be performed, and if you will involve a community advisory board. For research conducted outside the organization and its affiliates describe the site-specific regulations or customs affecting the research outside the organization and the local scientific and ethical review structure outside the organization.	☒ **Yes**
Resources Available*: Describe the resources available to conduct the research such us the feasibility of recruiting the required number of suitable participants within the agreed recruitment period; describe the time that you will devote to conducting and completing the research; describe the availability of medical or psychological resources that participants might need as a result of an anticipated consequences of the human research; describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.	☒ **Yes**
Multi-Site Research when Emory is the Lead Site: Study -Wide Number of Participants: indicate the total number of participants to be accrued across all sites.	☒ **Yes**

Study-Wide Recruitment Methods: If this is a multicenter study and participants will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.
Describe when, where, and how potential participants will be recruited.
Describe the methods that will be used to identify potential participants.
Describe materials that will be used to recruit participants.
Describe the processes to ensure communication among sites. See "WORKSHEET: Communication and Responsibilities (HRP-830)." All sites have the most current version of the protocol, consent document, and HIPAA authorization.
All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
All local site investigators conduct the study in accordance with applicable federal regulations and local laws.
All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy
Describe the method for communicating to engaged participating sites (see "WORKSHEET: Communication and Responsibilities (HRP-830)"):

- Problems (inclusive of reportable events).
- Interim results.
- The closure of a study

If this is a multicenter study where you are a participating site/investigator, describe the local procedures for maintenance of confidentiality. (See "WORKSHEET: Communication and Responsibilities (HRP-830).")

- Where and how data or specimens will be stored locally?
- How long the data or specimens will be stored locally?
- Who will have access to the data or specimens locally?
- Who is responsible for receipt or transmission of the data or specimens locally?
- How data and specimens will be transported locally?