Title: Use of Continuous Glucose Monitoring (CGM) in End-Stage Renal Disease (ESRD) Patients with Type 2 Diabetes

NCT# NCT04473430

Date: 05/29/2022

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Protocol Number: N/A
National Clinical Trial (NCT) Identified Number:
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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1 Phase Aim 1	Up to 100 subjects may be recruited, until a total of 40 insulin-treated patients with DM2 on hemodialysis have completed all procedures for this aim 1.	**Many patients do not enter the study procedures after screening visit, or complete the study procedures after randomization.**
1.1 Phase Aim 2	Up to 100 subjects could be recruited/consented, until a total of 45 patients have completed all procedures for Aim 2 (including those patients consenting to Aim 1 wanting to continue to Aim 1).	**Many patients do not enter the study procedures after screening visit, or complete the study procedures after randomization.**
1.2 Study Schema	Total n= 100 subjects may be consented, until 40 subjects have completed all study procedure	**As described above**

4.1 Study Design	Up to 100 subjects may be recruited, until a total of 40 insulin-treated patients with DM2 on hemodialysis have completed all procedures for this aim 1.	**As described above**
5.1 Inclusion Criteria for Aim 1	Up to 100 subjects may be recruited, until a total of 40 insulin-treated patients with DM2 on hemodialysis have completed all procedures for this aim 1.	**As described above**
5.1 Inclusion Criteria for Aim 2	Up to 100 subjects could be recruited/consented, until a total of 45 patients have completed all procedures for Aim 2 (including those patients consenting to Aim 1 wanting to continue to Aim 1).	**As described above**
5.6.1 Study	STUDY INTERVENTION DESCRIPTION: UP TO 100 SUBJECTS MAY BE RECRUITED, UNTIL A TOTAL OF 40 INSULIN-TREATED PATIENTS WITH DM2 ON HEMODIALYSIS HAVE COMPLETED ALL PROCEDURES FOR THIS AIM 1.	**As described above**

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Use of Continuous Glucose Monitoring (CGM) in End-Stage Renal Disease (ESRD) Patients with Type 2 Diabetes
Study Description:	Diabetes affects up to 40% of patients with end-stage renal disease (ESRD). Diabetes management in the context of existing ESRD is challenging due to alterations on glucose metabolism, insulin sensitivity, and renal clearance of several medications. Thus, most patients with diabetes on dialysis are treated with insulin therapy, resulting in increased risk for hospitalizations for hypoglycemia, mortality, length-of-stay and hospitalization costs at a national level. In many instances, clinicians and patients need to make treatment decisions based on few point-of-care blood glucoses (POC BG) per day, which fails to detect asymptomatic and nocturnal hypoglycemia and are not a good indicator of the 24-hours glycemic excursions. Novel factory-calibrated continuous glucose monitoring (CGM) devices have shown improved accuracy and could fill the critical need for better glycemic monitoring systems in dialysis patients. In this proposal, we will use CGM **(Aim 1a)** to examine the prevalence of hypoglycemia, hyperglycemia and estimate glycemic variability patterns among patients with type 2 diabetes (DM2), treated with insulin and receiving hemodialysis, **(Aim 1b)** to assess the accuracy of the CGM in this specific cohort, and **(Aim 2a)** to assess the efficacy of real-time CGM data in preventing hypoglycemia and hyperglycemia. We anticipate that this study will provide novel insights into the glycemic exposure patterns among dialysis patients

and will provide preliminary data for future outcomes-based studies determining the best glycemic targets for this group. Dr. Umpierrez has created a multidisciplinary team with track record of NIH funding, led by Dr. Umpierrez, with expertise in glucose monitoring and research methodology, and Dr. Tuttle, who is an expert on clinical and translational studies in diabetic kidney disease. His scientific advisory committee includes experts in biostatistics and bioinformatics (Dr. Limin Peng, PhD), and in CGM technology (Dr. Roy Beck, MD, PhD). Drs. Tuttle and Beck are external advisors and will only have access to de-identified data once the statistician has performed the analyses requested by the principal investigator.

Objectives:

Aim 1a. To examine overall glycemic control, as measured by CGM and POC (standard of care), among ESRD patients with DM2 treated with insulin

Primary Endpoint:

Mean daily glucose, as measured by CGM and POC BG

Secondary Endpoints:

Incidence of hypoglycemia by POC BG and CGM (< 70 mg/dl), glycemic variability [% coefficient of variability (%CV), mean amplitude of glucose excursions (MAGE)], rates of asymptomatic, and nocturnal CGM-detected hypoglycemia (<70 mg/dl, < 54 mg/dl and equal to 40 mg/dl), % time in hypoglycemia (< 70 mg/dl, < 54 mg/dL), time (%) in target range (70-180 mg/dl) and time (%) in hyperglycemia (>180 mg/dL, >250 mg/dl), 10-90% glucose percentiles, and mean hourly interstitial glucose before, during and after dialysis

Aim 1b. To assess the accuracy of the CGM system, as determined by differences in mean absolute relative difference (MARD), compared to time-matched paired glucoses measured by POC BG (standard of care) and YSI 2900 analyzer glucose sample in patients with DM2 on dialysis

Primary Outcome: Mean absolute relative difference (%MARD, calculated as the average relative difference between CGM, POC BG and intra-dialysis YSI matched glucose pairs).

Secondary Outcomes: %MARD for glucoses <70 mg/dL, <54 mg/dL, 70-180 mg/dL, >180 mg/dL, >250 mg/dL, % MARD during non-dialysis and during dialysis hours. Proportion of CGM values within ±20% or ±20 mg/dL (%20/20) of reference glucose values <70 mg/dL, <100 mg/dL, >100 mg/dL and >250 mg/dL, and the analogous %15/15, %30/30. We will utilize the Clarke Error Grid (CEG) and Surveillance Error Grid (SEG) analysis to evaluate for clinical risk of CGM errors

AIM 2. To determine the efficacy of real-time CGM in preventing hypoglycemia among insulin-treated patients with DM2 on hemodialysis, compared to standard of care (POC BG)

Primary Outcomes: Differences in mean percentage time-in-hypoglycemia (< 70 mg/dL) during the intervention phase, compared

to control in both groups (i.e. intervention-control vs. control-intervention).
Secondary Outcomes: CGM-measured % time-in-range (70-180 mg/dL), % time in hypoglycemia (<54 mg/dL), % time in hyperglycemia (>180 mg/dL, >250 mg/dL), % coefficient of variation (%CV, MAGE), HbA1c, hospitalization or emergency room visits for hypoglycemia or diabetes ketoacidosis.

Endpoints: See above for each study aim

Study Population: *Adult patients with type 2 diabetes on hemodialysis will be identified, recruited, and consented from the dialysis units of Emory Dialysis Centers and Grady Healthcare.*

Phase:

Aim 1. In the prospective observational cohort study, we will determine daily glucose concentration, rates of hypoglycemia (overall, nocturnal and asymptomatic), hyperglycemia and GV measures detected by real-time CGM in patients treated by maintenance dialysis compared to POC BG (standard-of-care, as available). Up to 100 subjects may be recruited, until a total of 40 insulin-treated patients with DM2 on hemodialysis have completed all procedures for this aim 1. After obtaining informed consent (Aim 1a), we will collect baseline demographics, and available laboratory data and place a blinded CGM (Day 1) for 10 days. Subjects will complete a food record for three (3) days for caloric intake analysis, one (1) on a pre-dialysis day, one (1) on dialysis day and one (1) on the day after a dialysis day[65].
For Aim 1b, we will only include 25 subjects. Between day 5-9, during one hemodialysis session, we will collect a dialysis circuit blood sample, to be drawn at 0 (pre-dialysis) 30, 60, 90, 120, 150, 180, 210, and 240 minutes and immediately after dialysis ends. Samples from the circuit will be analyzed using the YSI glucose analyzer. No therapy adjustment or interventions will be made by the study team during this period. Glycemic monitoring and treatment of dysglycemia will be performed by the primary care team following standard-of-care. Total duration: 10 days
Aim 2. In the cross-over, randomized, controlled trial, patients with type 2 DM treated with insulin, and on hemodialysis will use a real-time/personal CGM for 4 weeks (Intervention-Control Group), then 2 weeks of wash-out period, and cross over to use a blinded CGM for 4 weeks; and vice versa (Control-Intervention Group). Dexcom G6 monitors glucose continuously (24 hrs) and displays real-time glucose values, glucose trends/arrows and alarms, including the "urgent low soon" alarm (predictive of hypoglycemia < 55 mg/dL within the preceding 20 minutes). We hypothesize that the use of CGM will prevent hypoglycemia, and potentially rebound hyperglycemia, and consequently decreased glycemic variability during and between dialysis sessions in insulin-treated patients with type 2 DM. Total duration: 12-14 weeks. Up to 100 subjects could be recruited/consented, until a total of 45 patients have completed all procedures for Aim 2 (including those patients consenting to Aim 1 wanting to continue to Aim 1).

1.2 SCHEMA

Aim 1. Observational Study Process diagram

Day 0 — Screening (V1)

- Total n= 100 subjects may be consented, until 40 subjects have completed all study procedures
- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history and available laboratory data from electronic medical record
- After providing informed consent, patients will have a CGM sensor inserted by the study team (Day 1)
- Provide training materials and food record instrument.
- Subjects will be asked to complete a food record for three (3) days, one (1) on a pre-dialysis day and one (1) on the day after a dialysis day

Day 1-10 — Study Period

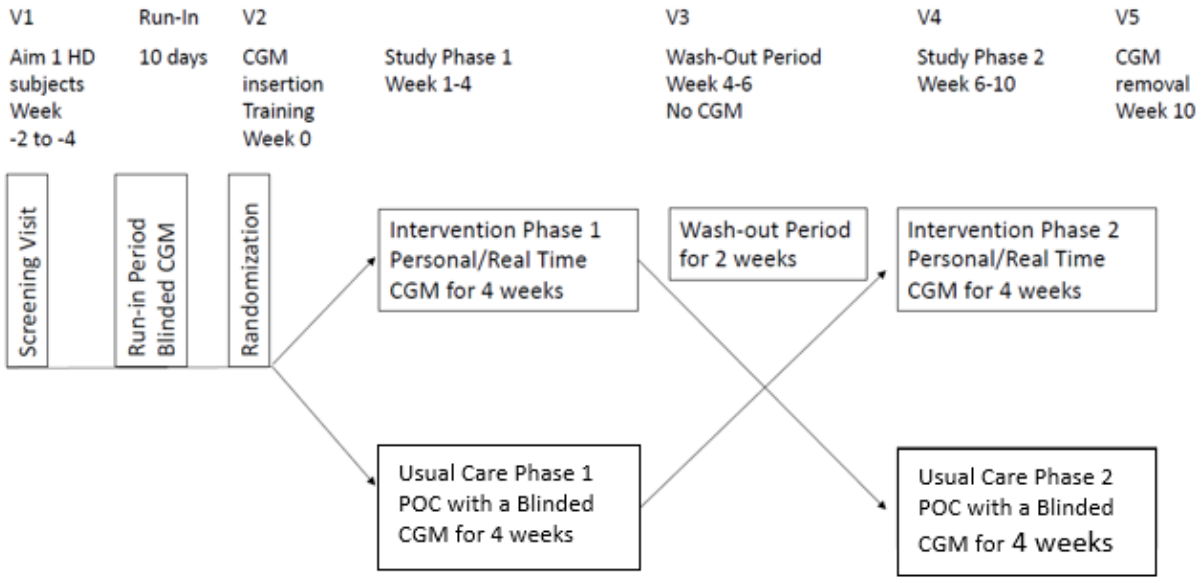
- Subjects will be instructed to perform self-monitored blood glucose (SMBG) four times daily at home during the study duration (10 days, as available), and to complete a DM diary (diabetic medications, food diaries, SMBG, etc.)
- Subjects will be asked to complete a one (1) time 8-point SMBG between days 5-9 days (Visit 2) after CGM insertion
- For Aim 1b: We will include only 25 subjects. Between day 5-9, during one hemodialysis session, we will collect a dialysis circuit blood sample, to be drawn at 0 (pre-dialysis), 30, 60, 90, 120, 150, 180, 210 and 240 minutes and immediately after dialysis. Samples from the circuit will be analyzed on the YSI glucose analyzer. Samples will be collected by the dialysis nurse, assisted by the study team. Samples from the circuit will be analysed on the YSI glucose analyser.

Day 10 — Final Visit (V3)

- Food record will be collected from the subject.
- On day 10, the CGM will be removed, and data download into Dexcom software. Glucose data from POC and venous testing will be paired with glucoses from the CGM (closest following value within 5 minutes)

Aim 2, RCT. Process Diagram

This will be a pilot, cross-over, randomized controlled trial, with an approximate duration of 12-14 weeks, as shown in figure below.



1.2 SCHEDULE OF ACTIVITIES (SOA)

Schedule of visits for Aim 2, Randomized Controlled Trial. See details on 6.1.1

Visit # (V)/ Phone visit (P)	V1	Run-In	V2	V3	Wash-Out	V4	V5
Time (weeks/days)[1]	-	N/A	0*	+4W	N/A	+6W	+10W
Inf. Consent	x						
Inc/exclusion	X		x				
Baseline CGM Insert[1]	X[2]						
Blinded CGM Collect			x				
Randomization			x				
Anthropometrics Measures	x			x			x
Laboratory	X[3]		x	x		x	x
Instruct SMBG	x		x	x		x	
Collect SMBG (as available)			x	x		x	x
CGM Use Training	x		x			x	
Blinded CGM Insert (Control Phase)[5]			x			x	
RT CGM insert (Intervention Phase)			X			X	
RT CGM Collect (Intervention Phase)				X			X
Insulin Adjust Training			X			X	
Diabetes Diary and Food Record[6]	x		x			x	
Hypoglycemia Training	x		x			x	
Adverse events			x	x		x	x
CGM accountability			X	x		x	x

[1]) Blinded CGM for all at baseline, [2]) Patients participating in Aim 1 (Observational Study) can enroll in Aim 2 (RCT) after completing the 10-days of blinded CGM, [3]) Baseline data collected from EMR, and Urine Pregnancy as indicated, [4]) Track insulin doses and meals, and complete one (1) food record for three (3) days. *Randomization visit +/- 7 days from completion of the running period.

2 INTRODUCTION

2.1 STUDY RATIONALE

Diabetes affects up to 40% of patients with end-stage renal disease (ESRD). Diabetes management in the context of existing ESRD is challenging due to alterations on glucose metabolism, insulin sensitivity, and renal clearance of several medications. Thus, most patients with diabetes on dialysis are treated with insulin therapy, resulting in increased risk for hospitalizations for hypoglycemia, mortality, length-of-stay and hospitalization costs at a national level. In many instances, clinicians and patients need to make treatment decisions based on few point-of-care blood glucoses (POC BG) per day, which fails to detect asymptomatic and nocturnal hypoglycemia and are not a good indicator of the 24-hours glycemic excursions. Novel factory-calibrated continuous glucose monitoring (CGM) devices have shown improved accuracy and could fill the critical need for better glycemic monitoring systems in dialysis patients. In this proposal, we will use CGM **(Aim 1a)** to examine the prevalence of hypoglycemia, hyperglycemia and estimate glycemic variability patterns among patients with type 2 diabetes (DM2), treated with insulin and receiving hemodialysis, **(Aim 1b)** to assess the accuracy of the CGM in this specific cohort, and **(Aim 2a)** to assess the efficacy of real-time CGM data in preventing hypoglycemia and hyperglycemia. We anticipate that this study will provide novel insights into the glycemic exposure patterns among dialysis patients and will provide preliminary data for future outcomes-based studies determining the best glycemic targets for this group.

2.2 BACKGROUND

A. Significance

A1. Burden of diabetes in ESRD patients: In 2015, there were over 700,000 patients with ESRD in the United States (U.S.)[1], with approximately 40% of patients having diabetes (DM) [2-4]. The adjusted survival is 55% and 40% after
3 and 5 years of hemodialysis initiation, with patients with DM having the worst adjusted survival rates[1,2,5,6]. Among 2,503 patients at Emory Dialysis Center during the last 8 years, up to 51% have diabetes: 80.1% receiving hemodialysis. Diabetes management in the context of existing ESRD is challenging due to altered glucose metabolism, insulin sensitivity, as well as altered renal clearance of several medications[7,8], resulting in increased risk for hypoglycemic and hyperglycemic events. In a national U.S.' database study of patients with diabetes on hemodialysis, hospitalized for hypoglycemia, we reported that ESRD was common (11.2%) and was associated with a 3-fold increase in mortality, longer length-of-stay (LOS) and hospitalization costs[9]. We also reported that ~10% of patients with diabetes on dialysis hospitalized with diabetes ketoacidosis had longer LOS and higher rates of treatment-related hypoglycemia than non-DM patients[10].

A2. Glycemic control assessment in patients with diabetes on dialysis.
Current guidelines recommend against strict glycemic targets, as measured by hemoglobin A1c (HbA1c), in patients with ESRD [4,11]. This recommendation is driven by the increased risk of hypoglycemia. In addition, HbA1c may not be accurate in the setting of advanced CKD and hemodialysis[3,12,13] and the optimal target HbA1c associated with best clinical outcomes in these patients is not well established[14]. Moreover, alternative glycemic markers, such as fructosamine or glycated albumin, have poor accuracy in certain situations (i.e. hypoalbuminemia), limited availability, and have not been extensively validated[3]. In most instances, clinicians and patients make treatment decisions -often insulin doses- based on point-of-care blood glucoses (POC BG). However, POC BG lacks accuracy, with just few glucose meters properly validated during

maintenance hemodialysis[15]. Moreover, the POC BG approach fails to detect asymptomatic and nocturnal hypoglycemia and fails to provide a complete glycemic profile throughout the day, particularly during dialysis sessions[16]. Hence, there is a critical need to find a standardized long-term outcome measure for glycemic control in dialysis patients, but also a glycemic measure that will allow patients and clinicians make rapid therapeutic decisions to prevent hypoglycemia[3,17]. New diabetes technology devices, such as continuous glucose monitoring (CGM), have the potential to become the new standard of care for assessment of glycemic control in dialysis patients; however, there are no studies assessing the efficacy and safety of the novel-factory calibrated sensors in this population.

A3. Management of Dysglycemia in Patients on Hemodialysis. Most anti-diabetic drugs require dose adjustments or are contraindicated in patients with advanced CKD or ESRD[3,4,7]. Thus, ~60-70% of patients with type 2 DM on hemodialysis are managed with insulin therapy[18-20], or with a combination of insulin and oral agents (sulfonylureas) which are associated with increased risk of adverse events[20]. In our institution, 56% of patients with type 2 DM are currently treated with insulin therapy, 37% received no therapy, and 7% are treated with oral agents: 40% secretagogues and 60% incretins. Notably, treatment with insulin and/or sulfonylureas is associated with a higher risk for emergency department (ED) visits and hospitalization for hypoglycemia among patients with ESRD[20]. In addition, hypoglycemia is associated with increased risk of cardiac arrhythmias[21], strokes[22], seizures[23], and sudden cardiac death[23,24]. Nevertheless, the evidence on the association between hypoglycemia and different anti-diabetic agents is limited[20,25]. In a small study (n: 10) of patients with type 2 diabetes and ESRD, Sobngwi et al. analyzed insulin needs during a euglycemic clamp and using short-term retrospective CGM[16]. The authors demonstrated that basal insulin doses decreased by 25% post-hemodialysis, compared to the pre-dialysis day. In a similar study using CGM, but in patients with no diabetes and ESRD, the same group reported a tendency towards lower glucose during the hemodialysis sessions, with a nadir at the 3rd hour[26]. However, no prospective intervention study has been performed using CGM to adjust insulin therapy in ESRD patients. We hypothesize that the high risk of hypoglycemia in this population relates to the high insulin and sulfonylurea utilization and to poor treatment dose adjustments due to lack of reliable glucose monitoring data to guide therapy.

A4. Use of continuous glucose monitoring (CGM) in insulin-treated patients with ESRD on hemodialysis. With the advent of CGM, we have recognized that hypoglycemia and glycemic variability are common events in patients with diabetes[27-31]. Even in patients with well-controlled T2D, Gehlaut et al found that 49% of patients had an asymptomatic hypoglycemic event detected byCGM[31]. Previous CGM studies in patients with CKD and ESRD are very limited due to the small numbers of patients and the short period (~72 hrs) of CGM evaluation[16,26,32-38]. Furthermore, prior CGM systems required calibration by finger stick POC BG, adding burden to the already high complex medical and personal care of this population. Recently, novel factory-calibrated systems have been approved for patients with type 1 DM and type 2 DM, requiring no finger-stick calibrations, and with excellent accuracy results [mean amplitude relative difference (MARD) <10%)][39]. Despite few studies supporting the benefits of CGM on overall glycemic control and hypoglycemia[40-42]; no prior studies have assessed the new factory-calibrated CGM systems in patients with ESRD. Accordingly, this proposal aims to 1) examine glycemic control, as measured by CGM, in ESRD patients with type 2 DM, compared to the standard of care (POC BG); 1b) assess the accuracy of the CGM system, as determined by differences in mean absolute relative difference (MARD), compared to time-matched paired glucoses measured by POC BG (standard of care) and to glucose measured by the gold-standard YSI 2900 analyzer in patients with DM2 on dialysis (n: 25); and 2) to determine the efficacy of real-time CGM in preventing hypoglycemia among insulin-treated patients with type 2 DM on hemodialysis, compared to the current standard of care POC BG.

A5. Novel factory calibrated CGM systems

The proposed CGM to be used in this study is the Dexcom G6, a factory-calibrated CGM system[43], that is innovative in many aspects: 1) it does not require finger stick POC BG for calibration, 2) the sensor is smaller, compact, light-weight, 3) has no interference with several substance and drugs, and 4) protective "urgent low soon" alarm, with proven prediction of hypoglycemia within 20 minutes in advance[39,44]. The sensor uses a novel semi-permeable membrane that blocks interference with most clinically relevant substances, including high levels of urea and creatinine, and commonly used medications[45,46]. This system could potentially eliminate the current high burden of patient and nursing care required for POC BG testing. We hypothesize that patients and clinicians will be able to prevent hypoglycemia – particularly asymptomatic and nocturnal hypoglycemia-, and potentially rebound hyperglycemia after treating hypoglycemic episodes, thus decreasing glycemic variability, by using easily available, continuous, real-time CGM data.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

1.a. Patients who develop hypoglycemia: We anticipate that ~50% of individuals recruited for this study will develop hypoglycemia by POC BG (as available).

During the observation study, blinded CGM data will be collected. Thus, subjects will be instructed to perform POC BG, as standard of care, for glucose monitoring. The study team will provide subjects with training on hypoglycemia management and prevention. If the study subject experiences hypoglycemic symptoms during the dialysis/blood glucose testing, we will notify the dialysis team to check a blood glucose and treat per standard of care. If POC BG or -YSI glucose is < 70 mg/dl, subjects will be given corrective measures, per standard of care, and communicate to their treating physician regarding subject's insulin doses and the need for follow-up for treatment of diabetes.

During the interventional study, all subjects will receive standard guidelines on how to adjust insulin based on CGM or POC BG data, and how to treat hypoglycemia per standard of care. The sensors provide a predictive hypoglycemia alarm ("predictive urgent low soon") that will alarm the subject within the preceding 20 minutes of a glucose < 55 mg/dl. The main objective of our RCT is to prevent hypoglycemia.

1.b. Risk of hyperglycemia.

We will exclude subjects with severe hyperglycemia (BG > 400 mg/dl) during consent/randomization. These subjects will be notified of the findings and advise to communicate with their treating physician for treatment adjustments.

1.c. Phlebotomy: Risks associated with phlebotomy and IV insertion are low and include small amounts of pain, possible bruising, swelling, redness, and rarely an infection at the site. However, we will collect blood from the pre-dialysis circuit and after the dialysis nurse inserted the dialysis needle. Approximately, ~5-10 ml of blood will be obtained during the dialysis for glucose testing (Aim 1b).These risks will be shared with the participants during informed consent and before starting the studies.

1.d. Sensor Insertion: We will use a commercially available (FDA approved) glucose sensor. 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.

1.e. Alternative Treatments and procedures. Patients with diabetes do not need to be part of this study. Monitoring POC BG is standard of care and all subjects in this study will be instructed to perform it. CGM is also indicated for monitoring glycemia and to assist with treatment adjustments in subjects with diabetes. This will be made clear before any subject signs the

informed consent. If subjects do not want to participate in the study, they will receive care that they are otherwise entitled to without bias.

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

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

2.3.2 KNOWN POTENTIAL BENEFITS

2.3.2.a Potential Benefit. Participation in the study may increase the subjects' awareness and improve the management of their diabetes. 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.

b. Risk of anticipated benefit. The risk associated with this study is minimal. We will take extensive precautions to reduce risks associated with phlebotomy (performed by dialysis nurse) and ensure that subjects' data remains confidential. The blood collection is minimal, and the amount is similar to that performed during a regular blood draw. Thus, the risk to benefit ratio favors conducting this study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

2.3.3. Subjects with diabetes on dialysis are exposed to wide glycemic excursions. The data obtained could help optimize treatment of this population subset, prevent future episodes of hypoglycemia, hyperglycemia and decrease glycemic variability. In this regard, the risks, which are small, would be outweighed by the benefit of knowledge and potential for a new standard of care for this cohort of patients

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1a. To examine overall glycemic control, as measured by CGM and POC (standard of care), among ESRD patients with DM2 treated with insulin	**Primary Endpoint:** Mean daily glucose, as measured by CGM and POC BG **Secondary Endpoints:** Incidence of hypoglycemia by POC BG and CGM (< 70 mg/dl), glycemic variability [% coefficient of variability (%CV), mean amplitude of glucose excursions (MAGE)], rates of asymptomatic, and nocturnal CGM-detected hypoglycemia (<70 mg/dl, < 54 mg/dl and equal to 40 mg/dl), % time in hypoglycemia (< 70 mg/dl, < 54 mg/dL), time (%) in target range (70-180 mg/dl) and time (%) in hyperglycemia (>180 mg/dL, >250 mg/dl), 10-90% glucose percentiles, and mean hourly interstitial glucose before, during and after dialysis	*Selected endpoints will provide a comprehensive glycemic profile, with detailed patterns of hypoglycemic and hyperglycemia excursions. These outcomes are endorsed by the American Diabetes Association International Consensus guidelines.*
Secondary		
Aim 1b. To assess the accuracy of the CGM system, as determined by differences in mean absolute relative difference (MARD), compared to time-matched paired glucoses measured by POC BG (standard of care) and to glucose measured by the gold-standard YSI 2900 analyzer in patients with DM2 on dialysis	**Primary Outcome:** Mean absolute relative difference (%MARD, calculated as the average relative difference between CGM, POC BG and intra-dialysis glucose measured by YSI, matched glucose pairs). **Secondary Outcomes:** %MARD for glucoses <70 mg/dL, <54 mg/dL, 70-180 mg/dL, >180 mg/dL, >250 mg/dL, % MARD during non-dialysis and during dialysis hours. Proportion of CGM values within ±20% or ±20 mg/dL (%20/20) of reference glucose values <70 mg/dL, <100 mg/dL, >100 mg/dL and >250 mg/dL, and the analogous %15/15, %30/30. We will utilize the Clarke Error Grid (CEG) and Surveillance Error	*These outcomes are endorsed by the American Diabetes Association International Consensus guidelines, and previously used in land-mark studies using CGM.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Grid (SEG) analysis to evaluate for clinical risk of CGM errors	
Tertiary/Exploratory		
AIM 2. To determine the efficacy of real-time CGM in preventing hypoglycemia among insulin-treated patients with DM2 on hemodialysis, compared to standard of care (POC BG)	**Primary Outcomes**: Differences in mean percentage time-in-hypoglycemia (< 70 mg/dL) during the intervention phase, compared to control in both groups (i.e. intervention-control vs. control-intervention). **Secondary Outcomes**: CGM-measured % time-in-range (70-180 mg/dL), % time in hypoglycemia (<54 mg/dL), % time in hyperglycemia (>180 mg/dL, >250 mg/dL), % coefficient of variation (%CV, MAGE), HbA1c, hospitalization or emergency room visits for hypoglycemia or diabetes ketoacidosis.	These outcomes are endorsed by the American Diabetes Association International Consensus guidelines, and previously used in land-mark studies using CGM. Real-time CGM use will prevent hypoglycemia, and potentially rebound hyperglycemia, and consequently decreased glycemic variability during and between hemodialysis sessions.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Aim 1a. To examine overall glycemic control, as measured by CGM and POC (standard of care, as available), among ESRD patients with DM2 treated with insulin. In this longitudinal cohort study, we will examine the overall glycemic control among insulin-treated patients receiving hemodialysis.

Hypothesis: Patients with DM2 on hemodialysis will have wide glycemic excursions, characterized by increased rates of symptomatic and asymptomatic hypoglycemia, with subsequent rebound hyperglycemic excursions and overall high glycemic variability.

Aim 1b. To assess the accuracy of the CGM system, as determined by differences in mean absolute relative difference (MARD), compared to time-matched paired glucoses measured by POC BG (standard of care) and YSI 2900 analyzer glucose sample in patients with DM2 on hemodialysis. In this comparative study, we will analyze glucoses obtained by CGM to the reference glucoses obtained by home POC BG and YSI obtained during dialysis sessions among subjects participating in Aim 1a.

Hypothesis: We hypothesize that the overall accuracy in patients with DM on dialysis will be within <12% MARD, compared to the standard of care POC BG and YSI .

Study Overview/Procedures for Aim 1a and Aim 1b:

In this prospective observational cohort study, we will determine daily glucose concentration, rates of hypoglycemia (overall, nocturnal and asymptomatic), hyperglycemia and GV measures detected by real-time CGM in patients treated by maintenance dialysis compared to POC BG (standard-of-care, as available). Up to 100 subjects could be recruited, until a total of 40 insulin-treated patients with DM2 on hemodialysis have completed all procedures for this Aim. After obtaining informed consent (Aim 1a), we will collect baseline demographics, and available laboratory data from the electronic medical record and place a blinded CGM (Day 1) for 10 days. Subjects will complete a food record for three (3) days for caloric intake analysis, one (1) on a pre-dialysis day, one (1) on dialysis day and one (1) the day after a dialysis day[65]. No therapy adjustment or interventions will be made by the study team during this period. Glycemic monitoring and treatment of dysglycemia will be performed by the primary care team following standard-of-care.

Study Design: The study team will perform pre-screening on subjects scheduled for their nephrology visits and will approach potential candidates by phone to determine interest and further qualification. If potential candidate expresses interest and qualifies for study participation, full consent procedure will be conducted during/after their hemodialysis sessions. After providing informed consent, patients will have a sensor inserted by the study team (Day 1, Visit 1). 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 on sensor, transmitter and receiver care. Subjects will be

instructed to perform self-monitored blood glucose four times daily at home during the study duration (10 days), and to complete a DM diary (diabetic medications, SMBG – as available-, food record, etc.) as well as to complete a Food record for three (3) days, one (1) on a pre-dialysis day, one (1) on dialysis day and one (1) the day after a dialysis day. Subjects will use their dialysis-validated glucose meter[15,66] and supplies, per standard of care. Subjects will be asked to complete a one (1) time 8-point SMBG between days 5-9 days after CGM insertion. For the 8-point SMBG, the study will provide a glucose meter with test strips (Nova Stat Strip). This is the glucose meter currently used at all Emory Hospitals.

For Aim 1b: In addition, a dialysis circuit venous blood sample (0.5 ml) for BG will be collected during one hemodialysis session as follows: at initiation, then every thirty (30) minutes, until the end of the dialysis session by the dialysis nurse, assisted by the study team. Samples from the circuit will be analyzed on the YSI 2300 glucose analyzer (visit 2). Similarly, capillary POC glucoses will be obtained at the same times, using the Nova Stat Strip glucose meter. CGM sensors that fail within the first 24 hours will be replaced, and the study will start again on Day 1 after re- insertion. On day 10, the CGM will be removed, and data download into Dexcom software (Visit 3). Glucose data glucoses from POC, venous testing will be paired with glucoses from the CGM (closest following value within 5 minutes). Food records will be collected.

Aim 2a. To determine the efficacy of real-time CGM in preventing hypoglycemia among insulin-treated patients with DM2 on hemodialysis, compared to standard of care (POC BG, as available). In this pilot, cross-over, randomized trial; insulin-treated patients with DM2 on hemodialysis will use a personal/real-time CGM for 4 weeks (Intervention), then after 2 weeks of wash-out period will cross over to use a blinded CGM (Control) for 4 weeks. Subjects will continue their regular capillary glucoses, as usually performed in clinical practice.

Hypothesis: Real-time CGM use will prevent hypoglycemia, and potentially rebound hyperglycemia, and consequently decreased glycemic variability during and between hemodialysis sessions.

Study Overview/Procedures (Randomized Controlled Study, RCT)

In this pilot, cross-over, randomized, controlled trial (Fig. 2), patients with type 2 DM treated with insulin, and on hemodialysis will use a real-time/personal CGM for 4 weeks (Intervention-Control Group), then 2 weeks of wash-out period, and cross over to use a blinded CGM for 4 weeks and continue to do their regular capillary glucoses, as usually performed in clinical practice; and vice versa (Control-Intervention Group). During the Usual Care/Control phase, subjects will wear a blinded/professional CGM for up to 4 weeks and continue to do their regular BG checks by capillary glucose, as usually performed in clinical practice. Participants will be trained to replace the G6 sensors at home during those 4 weeks, as usually performed in clinical practice. Dexcom G6 monitors glucose continuously (24 hrs) and displays real-time glucose values, glucose trends/arrows and alarms, including the “urgent low soon” alarm (predictive of hypoglycemia < 55 mg/dL within the preceding 20 minutes). We hypothesize that the use of CGM will prevent hypoglycemia, and the potentially rebound hyperglycemia, and consequently decreased glycemic variability during and between dialysis sessions in insulin-treated patients with type 2 DM. These results may provide novel data on glucose monitoring in this population that will serve as basis for future intervention studies to control hyperglycemia, while preventing hypoglycemia.

Study Design: In this cross-over RCT (Fig. 2), each subject will receive the intervention (24-hours real-time CGM) and conventional/standard-of-care therapy (POC BG, as available), at different study times. The cross-over design will reduce costs and simplify recruitment activities, while increasing power, since each subject will be studied with both treatment strategies and serve as controls. Dr. Galindo and Dr. Umpierrez have experience in RCT design, implementation and has previously published land-mark studies with a cross-over design[70]. There will be a wash-out period to avoid the potential carry-over effects of the CGM intervention, Phase I. Hypoglycemic excursions in hemodialysis patients treated with insulin are common, and thus 4 weeks of intervention with 2 weeks of wash-out period is expected to improve retention.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

See above Study Design

4.3 JUSTIFICATION FOR DOSE

N/A

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA, Section 1.3), or when all AEs have been resolved or considered ongoing but stable. Prior to this time, participants may voluntarily withdraw at any point in the study or the Investigator and/or Sponsor may determine that it is in the best interest of the participant to be terminated from the study.

Reasons for withdrawal of participant from the study include, but are not limited, to the following:

a) In the opinion of the Investigator, the participant's health or safety would be compromised by continuing in the study

b) In the opinion of the Investigator, it is in the participant's best interest to discontinue participation in the study

c) During the study, (female) participant becomes pregnant

Discontinuation of the study intervention (CGM) does not equate with discontinuation from the study and every effort will be made to retain participants in the study for the primary outcome assessment, even if CGM is discontinued.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:

AIM 1. Observational Study

a. Characteristics of the study population. We plan to investigate glycemic control, as measured by a blinded CGM, in 40 clinically stable subjects, between the ages of 18-80 years, with type 2 diabetes on chronic dialysis and treated with insulin therapy, willing to wear the CGM and perform SBMG as instructed. If needed, we will consent/recruit up to 100 subjects, until 40 subjects have completed all procedures for this aim. For Aim 1b, comparison of glucoses from CGM, POC (as available) and YSI, we will only recruit 25 subjects.

b. Inclusion Criteria Aim 1a/b: Ambulatory patients with type 2 diabetes, 18-80 years of age, willing to perform self-monitored blood glucose (SMBG) tests at home, HbA1c 5-12%, eGFR < 15 mL/min/1.73m2, receiving dialysis (hemodialysis) for at least 3 months, on insulin therapy [basal insulin alone (glargine U100, glargine U300, determir, degludec, NPH)], or in combination

with bolus insulin (at least one or more injections of aspart, lispro, glulisine, regular insulin) or in combination with incretin therapy (i.e. DPPIV inhibitors or GLP1 agonists).

AIM 2. Randomized Controlled Trial

a. Characteristics of the study population: Similar to Aim 1, we will primary recruit from the Emory Dialysis Center or Grady Memorial Hospital Dialysis Unit. Up to 100 subjects could be consented/recruited, until a total of 45 subjects with type 2 diabetes on hemodialysis treated with insulin have completed all procedures for this aim. Subject on hemodialysis, treated with insulin participating in Aim 1 will be invited to participate in the RCT, after completing the 10-days blinded CGM, if meeting all inclusion criteria.

b. Inclusion criteria Aim 2a: Adult subjects with type 2 diabetes, receiving hemodialysis at the Emory Dialysis Center or Grady Dialysis Unit (for at least 90 days), treated with insulin therapy [basal insulin alone (glargine U100, glargine U300, determir, degludec, NPH)], or in combination with bolus insulin (at least one or more injections of aspart, lispro, glulisine, regular insulin) or in combination with incretin therapy (i.e. DPPIV inhibitors or GLP1 agonists), willingness to wear the CGM, currently performing self-monitored blood glucose.

5.2 EXCLUSION CRITERIA

AIM 1. Observational Study

Exclusion Criteria Aim 1a/b: Critical medical or surgical illness, active malignancy with ongoing therapy, unable to give informed consent, severe hypoglycemia (BG < 40 mg/dL) or severe hyperglycemia (BG> 400 mg/dL) during randomization, pregnancy or breastfeeding, severe anemia (Hemoglobin < 5 mg/dl) or polycythemia (Hemoglobin >17 mg/dl), subjects taking acetaminophen (more than 1 gr every six hours) or hydroxyurea (may cause interference with the sensor membrane), taking secretagogues (glipizide, glyburide, glimepiride, repaglinide). Subjects who are sensitive or allergic to adhesive. Extensive skin changes/diseases that preclude wearing the required number of devices on normal skin (e.g., extensive psoriasis, recent burns or severe sunburn, extensive eczema, extensive scarring, extensive tattoos, dermatitis herpetiformis) at the proposed wear sites. Any condition that, in the opinion of the Investigator, would interfere with their participation in the trial (e.g., marked visual or hearing impairment, active alcohol or drug abuse, mental illness) or pose excessive risk to study staff handling venous blood samples. Situations that will limit the subject's ability to comply with the protocol (per investigator discretion), active malignancy, unable to give informed consent.

AIM 2. Randomized Controlled Trial

Exclusion criteria Aim 2a: Using sulfonylureas or thiazolidinediones alone or in combination with insulin. Use of personal/real-time CGM 3 months prior to study entry (blinded CGM is allowed), prior use of insulin pumps or hybrid close loop systems (for at least the prior 28 days), current or anticipated use of stress steroids doses (prednisone ≤5mg or its equivalent is allowed). Subjects who are sensitive or allergic to adhesive. Extensive skin changes/diseases that preclude wearing the required number of devices on normal skin (e.g., extensive psoriasis, recent burns or severe sunburn, extensive eczema, extensive scarring, extensive tattoos, dermatitis herpetiformis) at the proposed wear sites. Any condition that, in the opinion of the

Investigator, would interfere with their participation in the trial (e.g., marked visual or hearing impairment, active alcohol or drug abuse, mental illness) or pose excessive risk to study staff handling venous blood samples. Situations that will limit the subject's ability to comply with the protocol (per investigator discretion), active malignancy, unable to give informed consent, at least 10% of time spent in clinical relevant hypoglycemia (<54 mg/dl) during blinded CGM period, significant hypoglycemia (< 40 mg/dL) or severe hyperglycemia (BG> 400 mg/dL) during randomization, extensive skin abnormalities at insertion sites, pregnancy or breastfeeding, severe anemia (Hemoglobin < 5 mg/dl) or polycythemia (Hemoglobin >17 mg/dl), subjects taking acetaminophen (more than 1 gr every six hours) or hydroxyurea (may cause interference with the sensor membrane).

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in Aim 1 and Aim 2 of the study but are not subsequently assigned to the study intervention or entered in the study.

For Aim 1: Failing to meet inclusion criteria (laboratory and/or failing to perform SMBG)

For Aim 2: Individuals who do not meet the criteria for participation in this trial (screen failure) because of acute illness, hospitalizations or transiently not receiving dialysis may be rescreened (1 additional time). Rescreened participants should be assigned the same participant number as for the initial screening. Subject with sensor malfunctioning [less than 70% usage (e.g. at least 7 days of CGM readings collected). Subjects that did not perform SMBG (average of 1-2 times per day during the 10-day baseline blinded CGM period) will be considered screen failures, per investigator discretion.

In the event the participant was unable to collect a minimum of 7 days of CGM data due to device issues, not compliance issues (i.e., adhesive or sensor failures) they may have their sensor wear run-in period extended in order to collect the required number of days. This extension will be at the discretion of the investigator.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential candidates will be identified, and informed consent will be obtained during their visits to the Emory and Grady Dialysis Center. Enrollment will be coordinated with the nephrology faculty caring for these patients. Emory's nephrology faculty provided services to over 800 patients at The Emory Dialysis Centers in 2018, including 51% (n: 380) of patients with diabetes. Among those, 88% (n: 335) and 11.8% (n: 45) were receiving hemodialysis and peritoneal dialysis, respectively. We will recruit adults (older than 18 years of age) males and females of all races and ethnic backgrounds.

No vulnerable populations will be studied. The study will not involve populations such as fetuses, neonates, pregnant women, children under the age of 18 years, institutionalized individuals, or others who may be considered as vulnerable populations. If a subject becomes

incarcerated during the study, develops a serious medical or psychiatric illness during the study, they will be disqualified from participating further in the study. It will however recruit subjects on chronic dialysis and elderly subject between the ages of 65 to 80 years of age. Dr. Umpierrez have vast experience recruiting for several studies of patients with diabetes. All the proposed aims will take place at Grady Memorial Hospital, Emory University Midtown Hospital and Emory-Grady Dialysis Centers. Dr. Janice Lea, Chief Medical Director of the Emory Dialysis Center will assist with recruitment logistics. We also plan to enroll participants from the regional/local Davita Dialysis centers, with the assistance of Dr. Luis Pimentel, a board-certified nephrologist and long-time collaborator of our research group.

STUDY INTERVENTION

5.6 STUDY INTERVENTION(S) ADMINISTRATION

5.6.1 STUDY INTERVENTION DESCRIPTION

Aim 1. Study Overview/Procedures for Aim 1a and Aim 1b: In this prospective observational cohort study, we will determine daily glucose concentration, rates of hypoglycemia (overall, nocturnal and asymptomatic), hyperglycemia and GV measures detected by real-time CGM in patients treated by maintenance dialysis compared to POC BG (standard-of-care, as available). Up to 100 subjects maybe consented/recruited, until a total of 40 insulin-treated patients with DM2 on hemodialysis have completed all procedures for this aim. After obtaining informed consent (Aim 1a), we will collect baseline demographics, and available laboratory data and place a blinded CGM (Day 1) for 10 days. Subjects will complete a food record for three (3) days for caloric intake analysis, one (1) on a pre-dialysis day, one (1) on dialysis day and one (1) after a dialysis day[65]. No therapy adjustment or interventions will be made by the study team during this period. Glycemic monitoring and treatment of dysglycemia will be performed by the primary care team following standard-of-care. These results will provide detailed understanding of glycemic excursions among patients treated with insulin on hemodialysis. The information collected in these studies will be used as preliminary data for future intervention studies to control hyperglycemia, hypoglycemia and GV.

Study Design:
The study team will perform pre-screening on subjects scheduled for their nephrology visits and will approach potential candidates during/after their hemodialysis sessions. After providing informed consent, patients will have a sensor inserted by the study team (Day 1). Insertion of the CGM sensor will be performed per manufacture 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 on sensor, transmitter and receiver care. Subjects will be instructed to perform self-monitored blood glucose four times daily at home during the study duration (10 days), and to complete a DM diary (diabetic medications, food record etc.). Subjects will use their dialysis-validated glucose meter[15,66] and supplies, per standard of care. Subjects will be asked to complete a one (1) time 8-point SMBG between days 5-9 days after CGM insertion. In addition, a dialysis circuit venous blood sample (0.5 ml) for BG will be collected during one hemodialysis session as follows: at initiation, then every thirty (30) minutes, until the end of the dialysis session by the dialysis nurse, assisted by the study team. Samples from the circuit will be analyzed on the YSI 2900 glucose analyzer (visit 2). Sensors that fail within the first 24 hours will be replaced, and the study will start again on Day 1 after insertion. On day 10, the CGM will be removed, and data download into Dexcom software. Glucose data from POC will be

collected (as available).Venous testing will be paired with glucoses from the CGM (closest following value within 5 minutes) and POC. Food record will be collected.

Description of Study Visits for Aim 1a/b: The study team will perform pre-screening on subjects scheduled for their dialysis visits and will approach potential candidates during/after their hemodialysis sessions, at least 12 hours before starting dialysis. After providing informed consent, patients will have a sensor inserted by the study team (V 1). 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 on sensor, transmitter and receiver care. Subjects will be instructed to perform self-monitored blood glucose four times daily at home during the study duration (10 days), and to complete a DM diary (diabetic medications, food record, etc.). Subjects will complete a food record for three (3) days for caloric intake analysis, one (1) on a pre-dialysis day, one (1) on dialysis day and one (1) after a dialysis day. Subjects will use their dialysis-validated glucose meter (Abbott Freestyle Freedom/Lite, Ascencia/Bayer Contour Next, LifeScan One Touch Ultra) and supplies, per standard of care. Subjects will be asked to complete a one (1) time 8-point SMBG between days 5-9 days after CGM insertion. For the 8-point SMBG, the study will provide a glucose meter with test strips (Nova Stat Strip). This is the glucose meter currently used at all Emory Hospitals.

For Aim 1b, we will include only 25 subjects. In addition, a dialysis circuit venous blood sample (0.5 ml) for BG will be collected during one hemodialysis session as follows: at initiation, then every thirty (30) minutes, until the end of the dialysis session by the dialysis nurse, assisted by the study team. Samples from the circuit will be analyzed on the YSI 2900 glucose analyzer (visit 2).. Similarly, capillary POC glucoses will be obtained at the same times, using the Nova Stat Strip glucose meter. Sensors that fail within the first 24 hours will be replaced, and the study will start again on Day 1 after insertion. On day 10, the CGM will be removed, and data download into Dexcom software. Glucose data glucoses from POC will be collected (as available). Venous testing will be paired with glucoses from the CGM and POC (closest following value within 5 minutes). Food record will be collected.

Aim 2. Study Overview/Procedures (Randomized Controlled Study, RCT): In this pilot, cross-over, randomized, controlled trial (Fig. 2), patients with type 2 DM treated with insulin, on hemodialysis will use a real-time/personal CGM for 4 weeks (Intervention-Control Group), then 2 weeks of wash-out period, and cross over to use a blinded CGM for 4 weeks; and vice versa (Control-Intervention Group). Participants will be trained to replace the G6 sensors at home during those 4 weeks, as usually performed in clinical practice. Dexcom G6 monitors glucose continuously (24 hrs) and displays real-time glucose values, glucose trends/arrows and alarms, including the “urgent low soon” alarm (predictive of hypoglycemia < 55 mg/dL within the preceding 20 minutes). We hypothesize that the use of CGM will prevent hypoglycemia, and potentially rebound hyperglycemia, and consequently decreased glycemic variability during and between dialysis sessions in insulin-treated patients with type 2 DM. These results may provide novel data on glucose monitoring in this population that will serve as basis for future intervention studies to control hyperglycemia, while preventing hypoglycemia.

Study Design: In this cross-over RCT (Fig. 2), each subject will receive the intervention (24-hours real-time CGM) and conventional/standard-of-care therapy (POC BG), at different study

times. The cross-over design will reduce costs and simplify recruitment activities, while increasing power, since each subject will be studied with both treatment strategies, and serve as controls. Dr. Umpierrez have experience in RCT design, implementation and has previously published land-mark studies with a cross-over design[70]. There will be a wash-out period to avoid the potential carry-over effects of the CGM intervention, Phase I. Hypoglycemic excursions in hemodialysis patients treated with insulin are common, and thus 4 weeks of intervention with 2 weeks of wash-out period is expected to improve retention

Description of Study Visits for Aim 2a.

Screening Visit (weeks -2 to -4): Patients on maintenance hemodialysis treated with insulin will be invited to participate. Subjects enrolled in Aim 1a will be invited, if eligible, after completing the 10-days blinded CGM. After providing informed consent, patients will have a sensor inserted by the study team (V 1). Insertion of the CGM sensor will be performed per manufacture 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 on sensor, transmitter and receiver care. Participants will be trained to replace the G6 sensors at home during those 4 weeks, as usually performed in clinical practice. We will collect baseline demographics, and available laboratory data (HbA1c, glucose, creatinine/BUN, hemoglobin, and hematocrit), current medications and Kt/V (dialysis adequacy test) from the electronic medical record. Subjects will be instructed to perform self-monitored blood glucose four times daily (SMBG, as available) at home during the study duration (10 days), and to complete a DM diary (diabetic medications, food record). Subjects will use their dialysis-validated glucose meter, per standard of care. During this visit, participants will receive training on CGM use and POC BG diary completion. Subjects will bring their glucose meter, CGM sensor (if applicable), BG diary, to each onsite visit.

Run-In Period: Subject will perform their usual SMBG, and record data into the BG diary. Per investigator discretion, subjects may be excluded if they did not perform SMBG (during the 10-day period), or if the investigator determines that they will not wear the CGM for at least 70% of the intervention period (7/10 days).

Randomization (week 0) to Phase 1 (week 1-4): After 10 days, subjects will return for the blinded sensor removal. Transmitter will be connected to the computer for data downloading.

Intervention Group, Phase 1: A new personal/real-time CGM will be inserted. Patients will receive training on sensor care and how to use sensor's data (arrows, glucose trends and alarms) for diabetes management. A graphical display of trends, arrows and its significance will be given to all participants. Subjects will also receive **guidelines on how to adjust insulin therapy** using CGM or POC BG data.

Wash-Out Period (week 4-6): After completion of phase 1, all subjects will return to the clinic to remove the CGM and review the POC BG diary. After sensor removal, transmitter will be connected to the computer for data downloading. Sensor will be stored following standard precautions. Study personnel will input required clinical and demographic data into the sensor database software. During this period, no CGM will be worn, and all subjects will be reminded to perform self-monitored BG (SMBG) as usual.

Phase 2 (week 7-10): After completing the wash-out period, subjects initially randomized to the "Usual Care, Phase 1" arm will have a personal/real-time CGM inserted during the visit, and will be trained on how to use CGM to improve glycemic control (as described above)
Subjects initially randomized to "Intervention Group, Phase 1" will then cross-over to the "Usual Care Group, and a blinded CGM will be used for up to 4 weeks.

Last Visit (week 10): After completing the 4 weeks' assignment, subject will come back for CGM removal, if applicable. After sensor removal, transmitter will be connected to the computer for data downloading. Sensor will be stored following standard precautions. Study personnel will input required clinical and demographic data into the sensor database software

Guidelines to improve glycemic control using real-time CGM or POC BG:

Glucose Target	**Know your personal glucose targets and take actions to reach them. My pre-meal target is 80 - 180 mg/dl. My post-meal target is < 200 mg/dl (2 hours after the start of a meal).**
Low Glucose (Hypoglycemia)	Plan to prevent or to respond to hypoglycemia. Check POC glucose for confirmation. Eat 15 grams of carbohydrates (4 ounces of apple juice, or 4 glucose tablets) and repeat a fingerstick blood glucose measurement 15 minutes later. Repeat treatment if glucose <100 mg/dl every 15 min until BG > 100 mg/dl. Do not inject until glucose > 100 mg/dL.
CGM - Risk of Hypoglycemia (Urgent Low Soon Alarm)	For the "Urgent Low Soon Alarm" (predictive of hypoglycemia <55 mg/dL, within the preceding 20 minutes): 1) Eat 15 grams of carbohydrates and recheck in 15 minutes, 2) avoid injecting insulin or taking anti-diabetic agents until glucose is higher than 100 mg/dL, 3) check POC glucose for confirmation, 4) collect data in the diary.
Basal Insulin Dose Adjustments	Adjust dose of basal insulin based on the prior 24-hours glucose values. If **hypoglycemia <70 mg/dL (at least once), reduce daily dose by 30% the day prior to dialysis, or by 20% during the dialysis day**[16].
Pre-Prandial Bolus Insulin Dose Adjustment	After 3 days, If pre-meal glucoses > 180 mg/dL: 1) increase insulin by 2 units before each meal. If glucose > 280 mg/dL in 3 consecutive days, increase insulin by 4 units and call study team.

Device Information: Dexcom G6 CGM

The proposed CGM to be used in this study is the Dexcom G6, a factory-calibrated CGM system[43], that is innovative in many aspects: 1) it does not require finger stick POC BG for calibration, 2) the sensor is smaller, compact, light-weight, 3) has no interference with several substance and drugs, and 4) protective "urgent low soon" alarm, with proven prediction of hypoglycemia within 20 minutes in advance[39,44]. The sensor uses a novel semi-permeable membrane that blocks interference with most clinically relevant substances, including high levels of urea and creatinine, and commonly used medications[45,46]. Dexcom G6 CGM is a commercially-available, minimally invasive sensor, with a flexible and thin wire that is inserted into the abdominal subcutaneous tissue. In addition, subjects will check their POC BG (standard of care) using commercially available glucose meters, approved to be used in dialysis populations. Medical history and demographics will be collected from the medical record.

5.6.2 DOSING AND ADMINISTRATION

See above Table for Aim 2

5.7 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

5.7.1 ACQUISITION AND ACCOUNTABILITY

The investigator will obtain the Dexcom G6 CGM packages from the manufacturer and will provide it to all patients at no charge, as part of the study by the study team (PI, Co-PIs, Coordinators). After removal, data download, and stored, devices will be discard following standard precautions.

Investigational Device	**Total # returned to Site**	**Total # Used**	**Total # Used and Returned**	**Total # Unused and Returned**
CGM Sensors: Lot #:				
Reader:				

5.7.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The following performance specifications of the CGM System are applicable to the study:

Sample type:	Interstitial Fluid
Test sites:	Abdominal area (above beltline) and back of upper arm
Calibration requirements:	Not required
Wear use Life:	Up to 10 days
Range of measurement:	40-400 mg/dL
Humidity Range:	10-95% relative humidity
Altitude:	Up to 13,800 feet
CGM Sensor Useful Life:	3 months
Measured Parameter:	Interstitial Fluid Glucose

Packaging Information
Product Name
Catalog #
Lot #
Expiration Date
Date of Manufacture
Serial Number
Unique Device Identifier
Name and Address of Manufacturer

5.7.3 PRODUCT STORAGE AND STABILITY

Storage
Keep in its sterile packaging until you're ready to use it.
Store at temperatures between 36° F and 77° F.
Storing outside this range may cause inaccurate G6 readings.
May store sensor in refrigerator if it's within temperature range.
Store sensors in a cool, dry place. Don't store in parked car on a hot day or in freezer.

Transmitter
Keep protected when not in use
Store at temperatures between 32° F and 113° F
Store between 10% and 95% relative humidity

Receiver
Keep protected when not in use
Fully charge the battery before storing for over 3 months
Store at temperatures between 32° F and 104° F
Store between 10% and 95% relative humidity

5.7.4 PREPARATION

Installation of the CGMs:

The steps involved with the installation of the CGMs are as follows:

1. Participant will go to a private area
2. Study staff will clean your skin using an alcohol wipe and allow it to air dry.
3. The area of insertion will be shaved if clinical study staff determines that this is needed, you can use a shaving method of your choice. You may bring your own razor or electric shaver, or we will provide a disposable razor for you.
4. The study team will remove the CGM and Inserter Assemblies from their packaging.
5. The staff member will remove the adhesive backing from each Inserter Assembly. The adhesive backing is similar to the adhesive backing of a bandage.
6. The staff member will place each Inserter Assembly against your skin surface at the selected insertion site.
7. The staff member will then gently push down on the Inserter Assembly until he/she hears and feels a "Click" indicating the CGM has been inserted below the skin surface. At the time of CGM insertion you will feel a small prick similar to the insertion of a small needle.

8. The staff member will then gently remove the Inserter Assembly from the CGM leaving behind the CGM attached to your skin surface.
9. The staff member will then verify proper insertion and adhesion of the CGM to the skin surface.
10. Lastly, the staff member will explain the benefit of using a protective Overpatch over each of the CGMs for the duration of the study to prevent water damage and ensure adhesion to the attachment site. The decision to use a protective Overpatch will be your decision and is not a requirement of the clinical study.

If additional insertions are required in the event of an immediate CGM failure or failure that occurs during the study period, we will not attempt more than two (2) CGM insertions during the study period.

Once the CGMs have been successfully installed, the staff member will synch the internal Transmitters to two (2) Readers provided. Each Reader is used to display your interstitial blood glucose (sugar) values to you continuously.

The newly installed CGMs will take about 60 minutes to equilibrate after installation. During this time the staff members will prepare you for your first clinical study visit.

5.8 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Aim 2. RCT

Subjects will be randomly allocated to each study phase using a computer-generated randomization scheme provided by Dr. Limin Peng, Professor of Biostatistics. Subjects will be randomized by prior history of hypoglycemia (reported or on blinded CGM). One research member not included in our team will maintain the randomization table. Due to the nature of the intervention (e.g. real-time CGM data vs POC BG), this will be an open label RCT**.** However, subjects and investigator will have no real-time/direct access to the primary outcome data (percentage of time in hypoglycemic range) until completion of the study, and after the CGM data is downloaded. Investigators and study team will be masked until completion of all study phases are completed, and the large CGM dataset is analyzed.

5.9 STUDY INTERVENTION COMPLIANCE

Criteria for participants to continue with randomization are 1) willingness and ability to use the CGM device, 2) and CGM adherence, defined as a minimum of 70% usage (e.g. at least 7 days of CGM readings). The CGM data will NOT be shared with participants, clinicians at the research site, or the treating community clinician.

It is possible that sensors fall off, thus we will cover the sensor with Tegaderm Adhesive Films. In our practice, this decreases the fall off rate to <10%. Sensors that fail within the first 24 hours will be replaced, and the study will start again on Day 1 after insertion (replacement up to 2 times).

5.10 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report

Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. The study will not provide any study medications. Treatment will be determined by the treating physician.

For Aim 1, we will include subjects on dialysis treated with insulin therapy [basal insulin alone (glargine U100, glargine U300, determir, degludec, NPH)], or in combination with bolus insulin (at least one or more injections of aspart, lispro, glulisine, regular insulin) or in combination with incretin therapy (i.e. DPPIV inhibitors or GLP1 agonists). Subjects taking hydroxyurea (may cause interference with the sensor membrane), taking secretagogues (glipizide, glyburide, glimepiride, repaglinide).

For Aim 2, subjects treated with insulin therapy [basal insulin alone (glargine U100, glargine U300, determir, degludec, NPH)], or in combination with bolus insulin (at least one or more injections of aspart, lispro, glulisine, regular insulin) or in combination with incretin therapy (i.e. DPPIV inhibitors or GLP1 agonists). Subjects using sulfonylureas or thiazolidinediones alone or in combination with insulin. Use of personal/real-time CGM 3 months prior to study entry (blinded CGM is allowed), prior use of insulin pumps or hybrid close loop systems (for at least the prior 28 days), current or anticipated use of stress steroids doses (prednisone ≤5mg or its equivalent is allowed

5.10.1 RESCUE MEDICINE

The study will no supply rescue medication. Insulin doses will be adjusted during the trial.

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Participation in the clinical study will be terminated for each participant following the last visit or when all AEs have been resolved or considered ongoing but stable. Prior to this time, participants may voluntarily withdraw at any point in the study or the Investigator and/or Sponsor may determine that it is in the best interest of the participant to be terminated from the study.

Reasons for withdrawal of participant from the study include, but are not limited, to the following:

a) In the opinion of the Investigator, the participant's health or safety would be compromised by continuing in the study

b) In the opinion of the Investigator, it is in the participant's best interest to discontinue participation in the study

c) During the study, (female) participant becomes pregnant

However, discontinuation of the study intervention (CGM) does not equate with discontinuation from the study and every effort will be made to retain participants in the study for the primary outcome assessment, even if CGM is discontinued.

The clinical study in its entirety will be considered complete upon receipt of reports from study monitoring activities, completion of site closeout visits, and issuance of a clinical study report. The clinical study report will include all safety and efficacy data.

Insertion of the CGM sensor will be performed per manufacture 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.

6.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

See above 7.1

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

a) In the opinion of the Investigator, the participant's health or safety would be compromised by continuing in the study
b) In the opinion of the Investigator, it is in the participant's best interest to discontinue participation in the study
c) During the study, (female) participant becomes pregnant

Significant study intervention non-compliance

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for 2 consecutive visits
- CGM usage < 70% of sensor period

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 7 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 EFFICACY ASSESSMENTS

Aim 1a
Primary Outcome: Mean daily glucose, as measured by CGM and POC BG
Secondary Outcomes: Incidence of hypoglycemia by POC BG and CGM (< 70 mg/dl), glycemic variability [% coefficient of variability (%CV), mean amplitude of glucose excursions (MAGE)], rates of asymptomatic, and nocturnal CGM-detected hypoglycemia (<70 mg/dl, < 54 mg/dl and equal to 40 mg/dl), % time in hypoglycemia (< 70 mg/dl, < 54 mg/dL), time (%) in target range (70-180 mg/dl) and time (%) in hyperglycemia (>180 mg/dL, >250 mg/dl), 10-90% glucose percentiles, and mean hourly interstitial glucose before, during and after dialysis.

After obtaining informed consent (Aim 1a), we will collect from the electronic medical records the following information: Demographics (age, sex, ethnicity, height, weight, BMI, employment, educational level) medical history (length of diabetes, current medications, prior anti-diabetic medications, cause of renal disease, co-morbidities, smoking and surgical history), physical exam findings during study visits (blood pressure, height, weight), and characteristics included in the inclusion/exclusion criteria, following HIPAA rules. We will also collect available laboratory data (hemoglobin, hematocrit, hemoglobin A1c, creatinine, urea, uric acid, phosphorus, PTH, vitamin D, lipid panel).

Subjects will complete a food record for three (3) days for caloric intake analysis, one (1) on a pre-dialysis day, one (1) on dialysis day and one (1) after a dialysis day[65], with instructions provided by the study coordinators.

Aim 1b. In Aim 1b, we will perform accuracy comparisons (see below) between matched glucose pairs obtained by the CGM vs POC (standard of care, as available).
Primary Outcome: Mean absolute relative difference (%MARD, calculated as the average relative difference between CGM, POC BG and intra-dialysis YSI matched glucose pairs).

Secondary Outcomes: %MARD for glucoses <70 mg/dL, <54 mg/dL, 70-180 mg/dL, >180 mg/dL, >250 mg/dL, % MARD during non-dialysis and during dialysis hours. Proportion of CGM values within ±20% or ±20 mg/dL (%20/20) of reference glucose values <70 mg/dL, <100 mg/dL, >100 mg/dL and >250 mg/dL, and the analogous %15/15, %30/30. We will utilize the Clarke Error Grid (CEG) and Surveillance Error Grid (SEG) analysis to evaluate for clinical risk of CGM errors[68].
Dataset for analysis: Each venous or POC BG value (as available) will be paired with the following CGM value within 5 min; these matched pairs will form the analysis data set. YSI/POC matched pairs within the CGM reportable range of 40–400 mg/dL will be evaluated.

Aim 2.
Primary Outcomes: Differences in mean percentage time-in-hypoglycemia (< 70 mg/dL) during the intervention phase, compared to control in both groups (i.e. intervention-control vs. control-intervention).
Secondary Outcomes: CGM-measured % time-in-range (70-180 mg/dL), % time in hypoglycemia (<54 mg/dL), % time in hyperglycemia (>180 mg/dL, >250 mg/dL), % coefficient of variation (%CV, MAGE), HbA1c, hospitalization or emergency room visits for hypoglycemia or diabetes ketoacidosis.

We will collect baseline demographics, and available laboratory data (HbA1c, glucose, creatinine/BUN, hemoglobin, and hematocrit), current medications and Kt/V (dialysis adequacy test) from the electronic medical record, following HIPAA rules.

Subjects will be instructed to perform self-monitored blood glucose four times daily (4 point-SMBG) at home during the study duration (10 days), and to complete a DM diary (diabetic medications, food record). Compliance with SMBG will be quantified.

7.2 SAFETY AND OTHER ASSESSMENTS

Screening:
- **Anthropometric measures**
- **Vital signs** (e.g., temperature, pulse, respirations, blood pressure).

Follow-up
- **Assessment of study intervention adherence** or see Study Intervention Compliance, section 6.4 At least 70% of data (7days) after insertion of CGM
- **Administration of** food record (3 days), one (1) on a pre-dialysis day and one (1) on a dialysis day
- **Assessment of adverse events.** Describe provisions for follow-up of ongoing AEs/SAEs.

7.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether considered intervention related.

7.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.3.3 CLASSIFICATION OF AN ADVERSE EVENT

7.3.3.1 SEVERITY OF EVENT

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

7.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Probably Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Possibly Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal

relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Relationship of AE to the Test Device:
Probable: Good reasons and sufficient documentation to assume causal relationship
Possible: Causal relationship is likely and cannot be excluded
Unlikely: The event is most likely related to an etiology other than the trial treatment
Unknown: Unable to assess due to insufficient evidence, conflicting data or poor documentation.

Anticipated Adverse Events (AAE) are considered to be those known, in terms of nature, severity and frequency, to be associated with the use of the test materials.

Unanticipated Adverse Events (UAE) are defined as any adverse experience that is not identified in nature, severity or frequency in the general investigational plan or elsewhere in the current application.

7.3.3.3 EXPECTEDNESS

Anticipated Adverse Events (AAE) are considered to be those known, in terms of nature, severity and frequency, to be associated with the use of the test materials.

The following events have been identified as possible device-related adverse events of **sensor insertion and wear**:

- • Excessive pain or discomfort from either system deployment or during wear period (8 or greater on a 10-point Likert scale)
- • Excessive bleeding, defined as requires removal of the device to stop bleeding
- • Hematoma, defined as induration at the sensor insertion location (ecchymosis is a known consequence of needle skin puncture or pressure from sensor pod and will not be captured as an AE)
- • Edema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- • Erythema from sensor and/or adhesive tape that is significant and non-resolving within 48 hours of sensor pod removal
- • Local infection, defined as presence of pus at either sensor wire or sensor pod site
- • Sensor or introducer needle fracture during insertion/wear/removal

Information regarding device-related AEs that occur during the study will be entered into appropriate CRFs. Such information will include, at a minimum:

- Date of event
- Severity
- Outcome
- Resolution of event

PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

PI will record all reportable events with start dates occurring any time after informed consent is obtained until 15 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.3.4 ADVERSE EVENT REPORTING

See above

7.3.5 SERIOUS ADVERSE EVENT REPORTING

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 AEs 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.

7.3.6 REPORTING EVENTS TO PARTICIPANTS

Not applicable

7.3.7 EVENTS OF SPECIAL INTEREST

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. Include content in this section if applicable, otherwise note as not-applicable.

Describe any other events that merit reporting to the sponsor, study leadership, IRB, and regulatory agencies. For example, in oncology trials, secondary malignancies are often captured.

Include any other reportable events not already included in the previous sections, such as cardiovascular and death events, medical device incidents (including malfunctions), laboratory test abnormalities, and study intervention overdose.

7.3.8 REPORTING OF PREGNANCY

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.

7.4 UNANTICIPATED PROBLEMS

Unanticipated Adverse Events (UAE) are defined as any adverse experience that is not identified in nature, severity or frequency in the general investigational plan or elsewhere in the current application.

An unanticipated adverse device effect (UADE) is not expected to occur. An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, the informed consent document, other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of participants.

During the review of a reported SAE, if Clinical Affairs management with the Investigator input determines the severity or extent of the event was not cited in this protocol or associated protocol materials, and the event was classified as, 'possibly related' to the device, the event will be documented as an UADE. If the event is classified as an UADE, the Investigator must notify the IRB within fifteen (15) working days of the original SAE notification.

If determined that the UADE presents an unreasonable risk to participants, the investigators will terminate all investigations or parts of investigations presenting that risk as soon as possible, but not later than 5 working days after such determination is made and not later than 15 working days after IRB first receives notice of the original SAE.

7.4.1 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (Ups) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

7.4.2 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed about Ups on an individual level by the study team.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

For Aim 1a, we will summarize mean daily glucose, incidence of hypoglycemia, glycemic variability measures separately using CGM data and POC BG data and compare them

(between CGM vs. POC – as available) by using paired t-tests or Chi-square tests (or Fisher's exact tests, for incidence of hypoglycemia). Using CGM data, we will further compute and summarize the incidence of asymptomatic, and nocturnal CGM-detected hypoglycemia (<70 mg/dl, < 54 mg/dl and equal to 40 mg/dl), overall time in hypoglycemia (< 70 mg/dl, < 54 mg/dL), time (%) in target range (70-180 mg/dl) and time (%) in hyperglycemia (>180 mg/dL, >250 mg/dl), 10-90% glucose percentiles, and mean hourly interstitial glucose before, during and after dialysis.
For Aim 1b, we will assess the accuracy of CGM based on paired CGM and POC data or paired CGM and YSI data. We will calculate the overall MARD, as well as MARD stratified according to different glucoses ranges (e.g. MARD for glucose <70, 70-180, >180, >250 mg/dl). We will also employ Clarke Error Grid and Surveillance Error Grid methods to determine the clinical accuracy of Dexcom G6 as compared to the reference values from POC or YSI. The statistical analyses for **Aim 1** are mostly about calculating summary statistics for different glycemic control measures and accuracy measures. For the continuous primary outcome of Aim 1a, with a sample size of 40, the length of the confidence interval for the continuous outcome would be 0.64 times its standard deviation. There would be over 80% power to detect a mean difference equals to 0.46 times the standard deviation of the continuous outcome based on a two-sided paired t-test with alpha = 0.05.

For Aim 2, the primary outcome is percentage time in hypoglycemia range (glucose <70 mg/dL, as measured by CGM, see definitions above) during the last 10 days of each study phase. The study design for Aim 2a is a two by two cross-over design. To assess the effect of real-time (RT) CGM on the primary outcome, we will first compare the changes in percentage time in hypoglycemia range from the first study phase to the second study phase between the two randomization groups (i.e. intervention-control vs. control-intervention), using a nonparametric Wilcoxon-test. Such a test is equivalent to testing the difference in the primary outcome between the intervention of RT-CGM and the usual care of POC under the assumption that the carryover effects are the same for the two randomization groups. To estimate the effect of RT-CGM vs usual care of POC, we will further fit a nested three-way linear mixed model which appropriately accommodates the two by two cross-over study design while accounting for the effects of study phase and sequence of intervention and usual care. For continuous secondary outcomes, we will follow the same analysis plan presented for the primary outcome. For binary secondary outcomes (e.g. the incidence of hospitalization), we will compare the discrepancy in the binary outcome between the two study phases using logistic regression. We can further fit a generalized linear mixed model tailored to the two by two cross-over design to estimate the effect of CGM vs. POC on the binary secondary outcomes.

8.2 SAMPLE SIZE DETERMINATION

No preliminary data is available on ESRD patients with this device. Heinemann et al.[42] studied subjects with hypoglycemia treated with insulin. The authors reported medians and interquartile ranges of this outcome under RT-CGM or usual care. Based on these preliminary data, we approximated the standard deviation (SD) of our primary outcome under the normality assumption. This suggests 6.45% as a conservative upper bound for the SD. Assuming 10% attrition rate and 6.45% as the SD of the primary outcome, recruiting 45 subjects would give 90% power to detect a mean difference in percentage time in hypoglycemia range which equals 4.8%, based on a two-sided t-test for a two by two cross-over design, with alpha=0.05.

8.3 POPULATIONS FOR ANALYSES

- Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)
- Modified Intention-to-Treat Analysis Dataset (e.g., participants who use the CGM for at least 10 days of study intervention and/or have acceptable amount of follow-up outcome data)
- Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who use the CGM for at least 10 days of study intervention)
- Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period)

8.4 STATISTICAL ANALYSES

See above 9.1

8.4.1 PLANNED INTERIM ANALYSES

We plan to perform interim analysis on the primary endpoint every 6 months and/or when half of the subjects have been randomized. The trial will be stopped if there is evidence beyond a reasonable doubt of a difference in the rate of death (two-sided alpha level, <0.01) between the treatment groups.

8.4.2 SUB-GROUP ANALYSES

We will adjust the analysis of the primary endpoint based on age, sex, race/ethnicity or other demographic characteristic(s).

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

The Informed Consent Form must be approved by the IRB. The informed consent process fully apprises the subjects of the risks and benefits to them and to society for participating in the study. Each Subject must provide informed consent before participating in the study.

If the Subject understands and agrees to participate in the study, the Subject will sign and date the Informed Consent Form and the signature will be witnessed. Each Subject is given an unsigned copy of the Informed Consent Form. If a subject has questions about his/her rights, the subject may contact a member of the IRB.

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: Food record, Glucose diary, and SMBG log.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator and/or trained coordinator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to

carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- The trial will be stopped if there is evidence beyond a reasonable doubt of a difference in the rate of death (two-sided alpha level, <0.01) between the treatment groups.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Emory IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

Data collection records with personal identifiers will be stored in locked file cabinets and in secure HIPAA compliant web-based data collection system (RedCap). Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research records will be limited to clinical and research investigators, data and safety monitor board, research coordinator (TBD), and Emory University IRB. In addition, genetic data will be stored on secure computer networks with high security standards.

9.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

9.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Guillermo Umpierrez, MD	TBA
Emory University School of Medicine	Emory
69 Jesse Hill Jr. Dr., Atlanta, GA, 30303	69 Jesse Hill Jr. Dr., Atlanta, GA, 30303
4046687663	
geumpie@emory.edu	

9.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including diabetes management, chronic kidney disease and diabetes devices. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined.

9.1.7 CLINICAL MONITORING

The research team will use the self-monitoring form available from Emory Clinical Trials Audit and Compliance Audit. We will first perform a site monitoring once the first five (5) subjects have been enrolled in the trial, and at least every twelve months thereafter. Any deficiencies found by using this tool will be promptly reported. We will address all significant or repeated issues of noncompliance with a written corrective and preventive action (CAPA).

9.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the PIs will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.1.9 DATA HANDLING AND RECORD KEEPING

9.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.
Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the

electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a 21 CFR Part 11-compliant data capture system provided by the Emory University Office of Clinical Research. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

9.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within <specify number> working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

9.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers up to 12 months after the completion of the primary endpoint by contacting the Principal Investigator.

Dr. Umpierrez will ensure proper registration of the clinical trial and that results are submitted to "Clinicaltrials.gov", per Emory internal policy and as stated in the program. Data obtained from the observational study and clinical trial will be presented at national and local meetings, in a de-identified format. All final peer-reviewed publications will be placed in the digital archive in PubMed Central.

9.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ABBREVIATIONS

The list below includes abbreviations utilized in this protocol.

AE	Adverse Event
BG	Blood Glucose
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
YSI	Yellow Springs Instruments

9.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.0	08/17/2020	Replacing food recall by food diary/record, clarification on incretin therapy. Clarification on the dataset analysis timepoints. Blinded CGM for up to 4 weeks. Participants will be trained on how to replace/insert a CGM (sensors last for 10 days)	
2.1	11/17/2020	Changing A1C range to 5-12% for Aim 1 Observational Study Inclusion Criteria	
2.1	11/17/2020	Window period for Randomization visit to +/-7 days	
3.0	02/09/2021	Removing from the Synopsis, Overall Design and Inclusion Criteria, the phrase prior hypoglycemia episodes within 6 months. Replacing venous blood glucose (VBG) for YSI glucose sample from Synopsis, Background, Objectives and endpoints, Overall design Adding available laboratory data in Synopsis, Schema, Overall Design, Study Intervention Description, Efficacy Assessment. Adding the phrase Adding the phrase In addition, a dialysis circuit venous blood sample (0.5 ml) for BG will be collected during one hemodialysis session as follow: at initiation, then every thirty (30) minutes, until the end of the dialysis session by the dialysis nurse, assisted by the study team. Samples from the circuit will be analyzed on the YSI 2300 glucose analyzer (visit 2), to Synopsis, Schema, Overall Design, Study Intervention Description.	

4.0	04/12/2021	Adding as available to POC BG and SMBG. Removing the phrase at least 4 times a day to POC BG.	
5.0	02/18/2022	Adding local/Regional Davita Dialysis centers as an enrollment sites	
6.0	05/29/2022	Increasing the number of subjects to be consented/recruited, to allow completiong of 40 subjects for Aim 1a and 45 for Aim 2.	

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