PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

Recent advances in continuous glucose monitors (CGMs) and availability of commercial CGM products to patients with type 1 and type 2 diabetes has made the use of CGM more widespread (1). CGMs work by placing a probe underneath the skin of a patient, into the interstitial space. The probe is an electroenzymatic sensor which uses glucose oxidase to break down glucose to create hydrogen peroxidase and other elements. Hydrogen peroxidase then interacts with a base metal layer of the sensor and is oxidized, which results in release of electrons which creates a current. The current is proportional to the glucose concentration. The current is measured by the probe and transmits a calculated glucose concentration to a receiving device (2). Substances that are widely distributed in body water, and thereby present in the interstitial space, potentially affect this technology. Acetaminophen and aspirin are substances that are have been known to affect the accuracy of these devices (3); however, more recently developed CGMs such as the Dexcom G6, were able to demonstrate no interference by acetaminophen (4). Patients with end stage renal disease (ESRD) who are on intermittent hemodialysis (iHD) or peritoneal dialysis (PD) undergo fluid shifts between the interstitial fluid and intravascular space during dialysis treatments. They are also often uremic and have metabolic acidosis (5). These fluid shifts, uremia, acidosis, and volume overload (increase in interstitial fluid volume due to ESRD) have the potential to impact the performance of the most advanced and commercially available CGMs; however, use of CGM in these patients has not yet been studied (3). Moderate to severe CKD is associated with both increase in insulin resistance and decrease in insulin clearance, which results in often unpredictable and labile glucose concentrations and increased risk of hypoglycemia in these patients (6). Use of CGM, and potentially hybrid closed loop insulin delivery systems that are dependent on accurate continuous glucose monitoring, has the potential to improve glucose control and quality of life in these patients (7). We feel this study will be valuable in collecting preliminary data needed with the goal of validating the use of CGM in this patient population.

Objectives/Hypothesis

Our specific aim is to conduct a pilot study to evaluate the accuracy of continuous glucose monitors (CGM) in End Stage Renal Disease (ESRD) patients on intermittent hemodialysis (iHD). Accuracy will be assessed by calculating the mean absolute relative difference (MARD) between CGM values and concurrent finger stick or venous blood glucose (CBG) in these patients during hemodialysis, and on non-dialysis days.

Primary Hypotheses: The MARD between CGM sensor glucose and CBG will be larger on non-HD days than during dialysis.

Study Design: Biomedical

1. **Will controls be used?**

Yes – patients are their own controls.

► **IF YES, explain the kind of controls to be used.**

Accuracy of CGM during HD session will be compared to the accuracy of the CGM on the same patient when they are not in HD session.

2. **What is the study design?**

Prospective cohort study using blinded 10-day CGM in 30 ESRD patients on iHD who have a diagnosis of type 1 diabetes mellitus or type 2 diabetes mellitus. Will attempt to recruit approximately 15 participants who use insulin therapy though this is not exclusionary. Patients will be requested to perform finger stick blood glucose (FSBG) values using a study glucometer 7 times daily at home (before meals, 2 hours after meals, and at bedtime) for 10 days. A study team member will obtain approximately 12 blood samples from the existing HD IV line during each (three) HD session the CGM sensor is worn. These blood samples will be immediately processed using the *i-STAT System.* While the goal is to have the subject participate in three hemodialysis sessions, two sessions will be acceptable and not considered a study deviation.

3. **Does the study involve a placebo?**

No

► **IF YES, provide a justification for the use of a placebo**

Human Participants

Ages: 18+
Sex: Any
Race: Any

Subjects- see below

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

30 subjects

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

40%

3. **How many subjects will be enrolled at all sites?**

Up to 50 subjects

4. **How many subjects will sign a consent form under this UVa protocol?**

Up to 50 subjects.

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

- Ages 18+
- Type 1 diabetes mellitus on intermittent HD thrice weekly OR Type 2 diabetes mellitus on intermittent HD thrice weekly
- Willingness and ability to comply with scheduled visits and study procedures

2. List the criteria for exclusion

- Noncompliant with HD therapies
- Pregnant women
- Subjects with Hct < 30. This will be determined via the monthly blood draw that the subjects coordinate with entry into the study.

3. List any restrictions on use of other drugs or treatments.

- Hydroxyurea - has been known to interfere with current continuous glucose monitor sensors.

Statistical Considerations

1. Is stratification/randomization involved?

No

►**IF YES, describe the stratification/ randomization scheme.**

►**IF YES, who will generate the randomization scheme?**

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
_____ Other*:* Specify Answer/Response:

2. What are the statistical considerations for the protocol?

This is a prospective cohort study of 30 patients with diagnosis of Type 1 or Type 2 diabetes mellitus. The patients enrolled in the study will have a blinded CGM placed for 10 days which will measure interstitial glucose using above referenced electroenzymatic technology and record interstitial blood glucose every 5 minutes. The CGM sensor will be collected 10 days after placement of the sensor. The patients will also check venous blood glucose using a provided glucometer seven times daily on non-HD days. During HD sessions, a study team member will measure blood glucose with the use of an *i-STAT System* point of care machine approximately 10-12 times at the following intervals: q15 minutes x 90 minutes, q30 minutes x 60 minutes, then q60 minutes until HD finished. The results from the *i-STAT System* glucose measurements will be recorded in the study flowsheet. The study glucometers will record and store the results of finger stick blood glucose values which will be collected each day (10 days) after placement of the

sensor. The CGM sensors may be discarded by the study subject. CGM transmitters will be returned to the study team. .

The CGM and study glucometer data will be compared in the 30 patients to assess accuracy in between hemodialysis sessions (HD day + 1 [considered euvolemic] and HD day + 2 day [considered volume overloaded]). MARD will be calculated.

3. Provide a justification for the sample size used in this protocol.
This is a small pilot study to assess MARD (accuracy) of CGM in hemodialysis dependent patients with diabetes.

4. What is your plan for primary variable analysis?
Data scientists at the center for diabetes technology will use CGM, glucometer, and iStat data to calculate the MARD between sensor glucose and venous blood glucose for patients during hemodialysis, and between hemodialysis in different volume states.

5. What is your plan for secondary variable analysis?
Secondary outcomes include duration of HD, volume removed during HD therapy, Basic Metabolic Panel (BMP) prior to HD session including Co2, BUN, glucose, complete blood counts, medications, and daily weight.

6. Have you been working with a statistician in designing this protocol?
No

IF YES, what is their name?

7. Will data from multiple sites be combined during analysis?
No. , Only UVA patients will participate in this study.

7(a). Does the study involve randomization?
IF YES, will randomization be done at each site or among sites?
7(b). Has the sample size calculation considered the variation among sites?
7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?
7(d). Is there a common protocol used in all sites?

Study Procedures-Biomedical Research

1. What will be done in this protocol?
Screening (Visit 1):
Potential subjects will be approached during their regularly scheduled dialysis sessions at a UVA dialysis facility. Subjects may be contacted via telephone as well. The subject's provider or study

physician may introduce the study to the potential subject. If interested, a member of the study team will discuss the study in detail and obtain informed consent. Pre-screening inclusion/exclusion questions regarding their possible eligibility for the trial may be reviewed.

Upon consent, the study team member will review the subject's inclusion/exclusion criteria will be assessed by the study team to ensure criteria has been met. The study team member will review the subject's medical history and medications. A serum pregnancy test will be performed for women who are of child-bearing potential. If a subject is pregnant, they will be withdrawn from the study and be advised to seek further confirmation from their primary provider. If the subject meets all criteria, they may continue with the CGM training visit on the same day or at a later date. Fingerstick and *i-STAT System* blood glucose values are for study purposes only. Treatment recommendations will not be provided.

The most recent Hemoglobin A1c value that is collected for standard of care and is either dated prior to the study start date or within the data collection period if the duration between the collection date and study start date is greater than 3 months.

Day 1 (Visit 2):

Day 1 may occur on the same day as Screening. At the end of the subject's dialysis session, the study team will insert a DexCom G6 CGM sensor into the participant's abdomen and educate the subject on the use of the DexCom G6 CGM. The CGM will be blinded to both the study physician and participant during the course of study participation – there will be no visible readings during the subject's participation in the study. Selected study team members may incidentally see sensor values when downloading the CGM data. CGM supplies and CGM user's guide will be provided to the participant. Patients will be given a study glucometer, testing supplies, and a scale to measure body weight each day. They will be taught how to use the study glucometer and informed of the schedule for fingerstick monitoring that will occur during the 10 days of wearing the CGM. Subjects will also be asked to weigh themselves every morning with the study-supplied scale and record it in a study record.

Non-Dialysis Days (Days 2, 3, 7, 9, 10):

On days that the subject does not have dialysis, they will perform 7 fingerstick blood glucose tests using the study glucometer. These will be done before meals, after meals, and at bedtime. Subjects will be encouraged to use the study glucometer for any additional blood glucose values they wish to perform.

Subjects will weigh themselves every morning upon voiding and record the results in a study record.

Dialysis Days (Days 4, 6, 8, 11):

On days that the subject has dialysis, they will attend their regularly scheduled dialysis session and perform that run with no change from standard care. During the session, 10-12 samples (1.5

cc) of blood will be drawn from the HD line that is placed for usual care purposes. These samples will occur at approximately the following times:

0m, 15m, 30m, 45m, 60m, 75m, 90m, 120m, 150m, 210m, then every 60 minutes until the end of the dialysis session.

The blood samples will be used to perform a blood glucose test using an *i-Stat System*. The study team will record results and data obtained clinically for the subjects during this time including lab results (e.g. weekly basic metabolic panel, etc…), dialysis run information (including dextrose concentration of the dialysate), vital signs including height and weight, and other clinically relevant medical information. Estimated blood loss will be 20cc per HD session and 60cc per study period. Glucose values collected during the dialysis session will not be used for treatment purposes.

At Home:

Participants will perform 7 fingerstick blood glucose tests using the study glucometer. These will be done before meals, after meals, and at bedtime. Subjects will be encouraged to use the study glucometer for any additional blood glucose values they wish to perform.

Subjects will weigh themselves every morning upon voiding and record the results in a study record.

While the goal is to have the subject participate in three hemodialysis sessions, two sessions will be acceptable and not considered a study deviation.

Final Study Visit (Day 11)

At the final study visit, subjects will remove the CGM sensor from their abdomen. The sensor will be discarded. The CGM transmitter will be returned to the study team. They will discontinue all use of other study equipment (e.g. study glucometer, scale, etc…) and return all study supplies to the study team. Subjects will continue with their standard care for their end-stage renal disease and diabetes management.

The CGM equipment stores the blood glucose values on the transmitter. The study glucometer will be downloaded by study staff once the subject returns the equipment to the team.

Weigh diaries will be completed.

Fingerstick Schedule for Monday, Wednesday, Friday dialysis patients

Sensor placement will occur at the conclusion of the patient's Friday dialysis appointment with the following fingerstick schedule:

Friday (Day 1)	Saturday (Day 2)	Sunday (Day 3)	Monday (Day 4)	Tuesday (Day 5)	Wednesday (Day 6)	Thursday (Day 7)	Friday (Day 8)	Saturday (Day 9)	Sunday (Day 10)	Monday (Day 11)
Dialysis day. Place CGM sensor. Check FSBG before meals and at bedtime.	7 FSBG readings: before & after meals & at bedtime.	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Obtain 10-12 iStat glucose values during HD session: q15m x 90min, q30m x 60min, q60m until end of HD session; 7 FSBG readings: before & after meals & at bedtime	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Obtain 10-12 iStat glucose values during HD session: q15m x 90min, q30m x 60min, q60m until end of HD session; 7 FSBG readings: before & after meals & at bedtime	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Obtain 10-12 iStat glucose values during HD session: q15m x 90min, q30m x 60min, q60m until end of HD session; 7 FSBG readings: before & after meals & at bedtime	7 FSBG readings: before & after meals & at bedtime.	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Final study visit to return study supplies. No FSBGs.

Fingerstick Schedule for Tuesday, Thursday, Saturday dialysis patients

Sensor placement will occur at the conclusion of the patient's Saturday dialysis appointment with the following fingerstick schedule:

Saturday (Day 1)	Sunday (Day 2)	Monday (Day 3)	Tuesday (Day 4)	Wednesday (Day 5)	Thursday (Day 6)	Friday (Day 7)	Saturday (Day 8)	Sunday (Day 9)	Monday (Day 10)	Tuesday (Day 11)
Dialysis day. Place CGM sensor. Check FSBG before meals and at bedtime.	7 FSBG readings: before & after meals & at bedtime.	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Obtain 10-12 iStat glucose values during HD session: q15m x 90min, q30m x 60min, q60m until end of HD session; 7 FSBG readings: before & after meals & at bedtime	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Obtain 10-12 iStat glucose values during HD session: q15m x 90min, q30m x 60min, q60m until end of HD session; 7 FSBG readings: before & after meals & at bedtime	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Obtain 10-12 iStat glucose values during HD session: q15m x 90min, q30m x 60min, q60m until end of HD session; 7 FSBG readings: before & after meals & at bedtime	7 FSBG readings: before & after meals & at bedtime.	7 FSBG readings: before & after meals & at bedtime.	Dialysis day. Final study visit to return study supplies. No FSBGs.

2. **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

   This is not a treatment study. Subjects will discontinue use of study equipment and return all supplies to the study team. Subjects will continue with their usual care and management of their diabetes and end-stage renal disease.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**

   Research coordinator will check in with patient at each HD session (3 sessions) during study period to review protocol and assess compliance.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**

   If patient obtains <3 finger sticks per day, or misses one HD session, the patient will be considered non-compliant.

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