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Inpatient and post-hospital discharge assessment of glycemic control by capillary point-of-care glucose testing and by continuous glucose monitoring in insulin-treated patients with type 1 and type 2 diabetes: Dexcom G6 Observational Study

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Short Title: Dexcom G6 Observational Study

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I. RESEARCH OBJECTIVES AND SPECIFIC AIMS

Diabetes is reported in 20-34% of hospitalized adult patients in general medicine and surgery units [1,2]. The annual incidence of diabetes as any listed diagnosis has more than doubled during the past 2 decades to a total of 7.2 million hospital discharges, for a total of 43.1 million hospital days among U.S. adults [3,4]. A large body of literature has shown a strong association between diabetes and increased mortality and morbidity [1,5-8]. Clinical guidelines have recommended the use of basal bolus insulin regimens as the preferred management approach of non-ICU patients with diabetes [9-11], as it has been shown to be effective in improving glycemic control and reducing hospital complications [12-14]. However, hypoglycemia is a common adverse event of insulin therapy [15-18], with incidence rates ranging between 12% and 35% in randomized studies in non-ICU settings [14,19]. The development of hypoglycemia, like hyperglycemia, has been associated with higher rates of hospital complications, higher health care resource utilization, and hospital mortality [10,16,20-22].

Bedside point-of-care (POC) capillary glucose monitoring is the standard of care to assess glycemic control in the hospital. Diabetes guidelines recommend bedside capillary POC testing before meals and at bedtime to assess glycemic control and to adjust insulin therapy in the hospital [9,10,23]. Continuous glucose monitoring (CGM) measures interstitial glucose every 5-15 minutes, thus providing a more complete glycemic profile during 24-hours compared to standard POC glucose testing [24,25]. In a recent study of hospitalized patients with type 2 diabetes (T2D), we reported increased detection of both hypo- and hyperglycemic events with the use of CGM compare to the standard-of-care POC glucose testing. Patients were treated with basal-bolus regimen in conjunction with CGM use [24]. More than 50% of the hypoglycemic events occurred between dinner and breakfast; suggesting that many of these episodes would be missed by standard POC testing. Schaupp et al [26] reported that the number of nocturnal hypoglycemic episodes <3.9 mmol/L (70 mg/dl) was 15-fold higher, and the number of episodes >13.9 mmol/L (250 mg/dl) detected by CGM during night was 12.5-fold higher [24] compared to capillary POC glucose testing in general medicine patients with type 2 diabetes treated with a basal bolus insulin regimen for ≥ 3 days.

A recent panel of experts in inpatient diabetes care reported that CGM could more effectively identify trends toward hypoglycemia and hyperglycemia, allowing for better and safer management of patients with inpatient hyperglycemia [27,28]. Despite evidence supporting the use of CGM devices in hospitalized patients; clinical guidelines have been inconclusive in recommending the use of CGM in the hospital due to the lack of safety and efficacy outcome studies [27,29,30]. In recent years, the improvement in the accuracy of CGM sensors, as well as lack of interference with acetaminophen [31] and need for calibration [32], suggest that CGM technology could replace the finger-stick blood glucose monitoring in insulin treated patients in the hospital. Accordingly, we propose a pragmatic evaluation of the Dexcom G6 CGM proving their accuracy and clinical effectiveness is needed, which may facilitate the widespread adoption of this technology in the hospital setting.

We hypothesize that CGM will provide a more complete 24-hour assessment of glucose values during hospitalization and after hospital discharge improving detection of hypoglycemic and hyperglycemic events compared to POC glucose testing (standard of care) in patients with type 1 (T1D) and type 2 diabetes (T2D).

B. Specific Aims:

Aim 1. To determine differences in glycemic control, as measured by mean daily blood glucose and frequency of hypoglycemic and hyperglycemic events, between DexcomG6 CGM and POC BG testing in hospitalized patients with T1D and T2D treated with basal bolus insulin regimen.
Hypothesis: Glucose monitoring by CGM will improve detection of clinically significant hypoglycemia (<54 mg/dl) and severe hyperglycemia (>240 mg/dl) compared to standard POC testing in insulin-treated patients with T1D and T2D.

Aim 2. To determine differences in glycemic control and accuracy after hospital discharge between DexcomG6 CGM and POC BG testing in hospitalized patients with T1D and T2D.

Hypothesis: Glucose monitoring by CGM will improve detection of clinically significant hypoglycemia (<54 mg/dl) and severe hyperglycemia (>240 mg/dl) compared to standard POC after hospital discharge in patients with T1D and T2D.

II. BACKGROUND AND STATUS OF WORK IN THE FIELD.

II.a. Inpatient glycemic control in non-ICU setting. Patients with diabetes have a three-fold greater chance of hospitalization compared to those without diabetes [33]. The annual incidence of diabetes as any listed diagnosis has more than doubled during the past 2 decades to a total of 7.2 million hospital discharges for a total of 43.1 million hospital days among U.S. adults affected [3,4]. Current guidelines recommend the use of intravenous insulin in the ICU and subcutaneous insulin regimens in non-ICU settings [10,34]. Although effective in improving glycemic control and in reducing hospital complications [14,35], intensive insulin therapy results in frequent hypoglycemia, reported in 12% to 30% of patients [13,36,37]. Thus, improving glycemic control while minimizing the rate of hypoglycemia is of major importance in the hospital, because both hyperglycemia and hypoglycemia have been shown to be independent risk factors of poor clinical outcome and mortality [1,38,39].

II.b. Transition Care from Hospital to Home. Hospital discharge represents a critical time for ensuring a safe transition to the outpatient setting and reducing the need for emergency department visits and re-hospitalization. Few studies have addressed the management of patients with diabetes after hospital discharge in insulin treated patients with T2D. In two recent randomized studies we assessed the efficacy of a hemoglobin A1c (HbA1c) based algorithm using glargine insulin for the management of patients with T2D [12]. Patients were discharged on a combination of oral antidiabetic drugs (OADs) and glargine insulin at 50% of hospital dose if their HbA1c was < 9%. Patients with an HbA1c ≥ 9% were discharged on a combination of OAD and glargine insulin at 80% of total daily hospital dose or on a basal bolus regimen with glargine and rapid-acting insulin analog before meals. The admission HbA1c on admission of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge. The rate of hypoglycemia was ~32% in patients treated with oral agents plus basal insulin and greater than 40% in patients treated with basal bolus insulin regimen. These RCT studies and previous retrospective studies highlight the importance of BG monitoring and cautious use of insulin after hospital discharge.

II.c. Use and limitations of CGM in non-ICU setting. Several studies have shown that the inpatient use of CGM is more effective in identifying trends toward hypoglycemia and hyperglycemia compared to standard POC glucose testing [24,25]. In a recent study of hospitalized patients with T2D, we reported increased detection of both hypo- and hyper- glycemic events with the use of CGM compare to the standard-of-care POC BG (23). There was no difference in mean daily blood glucose concentration between groups. CGM detected most hypoglycemic events, only one of which was detected on POC monitoring. More than 50% of the hypoglycemic events occurred between dinner and breakfast; suggesting that many of these episodes would be missed by standard POC testing. A recent panel of experts in inpatient diabetes care reported that CGM could more effectively identify trends toward hypoglycemia and hyperglycemia, allowing for better and safer management of patients with inpatient hyperglycemia (22). Significant limitations; however, are noted with the use of CGM in the hospital including 1) most studies used blinded CGM and therefore interventions to prevent impending hypoglycemia were not performed [25,26,40,41]; 2) glucose values captured in the CGM device are not transmitted to the nursing station to allow providers to detect and treat impending hypoglycemia; 3) hypoglycemia alarms are only visible and audible at the bedside; 4) lack of studies using CGM to guide insulin therapy in patients with diabetes, with minimal data on T1D patients [42].

We proposed a comprehensive research program to investigate the role of CGM (Dexcom G6 CGM) in the management of patients with diabetes in non-ICU setting receiving insulin treatment. The Dexcom G6 hospital research program includes two studies:

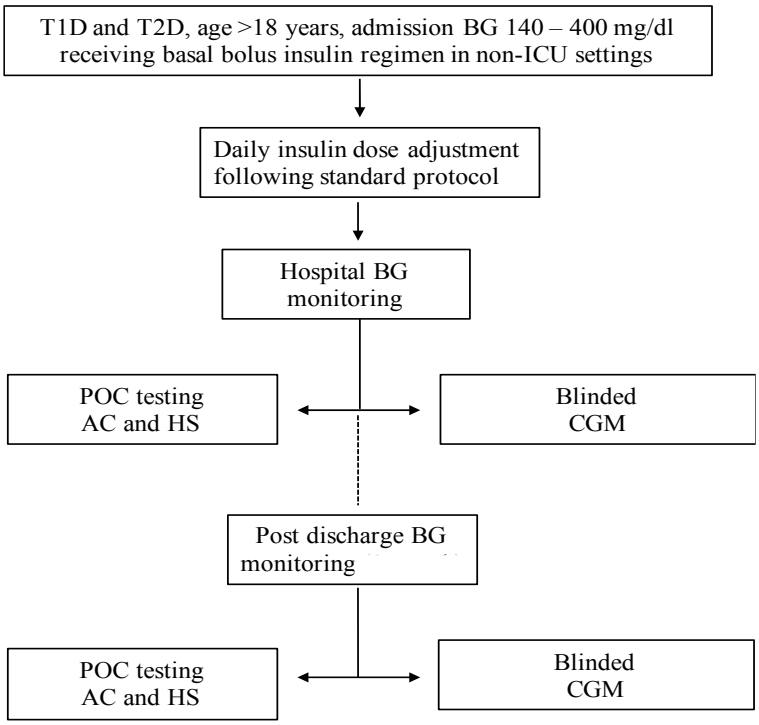
Study 1. Assessment of glycemic control in hospitalized insulin-treated patients with T1D and T2D by capillary point-of-care testing and continuous glucose monitoring: Dexcom G6 Observational Study

Study 2. Efficacy of Dexcom G6 continuous glucose monitoring in guiding insulin therapy in hospitalized patients with T1D and T2D: Dexcom G6 Hospital Intervention Trial.

Study 1, the current proposal is a pilot, exploratory observational prospective study aiming to evaluate the feasibility of using the Dexcom G6 CGM in the hospital to obtain preliminary estimates on differences in glycemic control, as measured by mean daily blood glucose and frequency of hypoglycemic and hyperglycemic events, compared to capillary POC BG testing (standard of care) in hospitalized patients with T1D and T2D treated with basal bolus insulin regimen. Treatment interventions will be made based on the current standard-of-care POC BG monitoring.

Patients with T1D and T2D who are expected to be hospitalized for longer than 3 days will wear the CGM and undergo POC testing before meals and bedtime (standard of care) during the hospital stay and after hospital discharge for 10 days. Patients will wear a CGM in the current approved insertion site, the abdomen, and in the upper arm both during hospitalization and then for 10 days post-discharge. Patients and the research team will be blinded to the CGM glucose results during the study. Downloading of the sensors will be performed at the day of discharge and 10 days after hospital discharge.

Study Diagram:



The Dexcom G6 CGM is a commercially available factory-calibrated sensor system [32], thus there is no need for POC BG testing for sensor calibration. Clinical data for 7-day stability have reported excellent correlation with glucose values reported by laboratory and POC testing. Although the benefits of factory-calibrated CGM sensors include replacing the need for finger-stick blood glucose monitoring and providing the benefits of real-time glucose values, its benefits and safety have not yet been proven in the hospital setting. It is important to mention potential limitations, including: the need for removing the sensor before MRI or diathermy treatment, and the potential interference in patients with severe dehydration.

III. STUDY DESIGN AND METHODS

Aim 1. To determine differences in glycemic control, as measured by mean daily blood glucose and frequency of hypoglycemic and hyperglycemic events, between DexcomG6 CGM and POC BG testing in hospitalized patients with T1D and T2D treated with basal bolus insulin regimen.

Patients: Patients with T1D and T2D will be included in this pilot, prospective observational study to determine differences in BG control by the Dexcom G6 CGM and POC testing before meals and bedtime (standard of care) during the hospital stay and after hospital discharge for 10 days. Two CGM devices will be inserted in all patients – one in the abdomen and one in the arm to also assess differences in BG readings between upper extremity and abdominal insertion sites.

We will recruit a total of 100 male and female subjects >18 years with T1D and T2D treated with basal bolus insulin regimen. Due to the design of this study, there will be no run-in period. Upon arrival to the emergency department or medical or general surgical wards, subjects will be screened. Patients with a known history of T1D and T2D treated with insulin and expected to be hospitalized for longer than 3 days will be considered potential candidates for this study. Patients admitted with acute or chronic medical illnesses, emergency or elective surgical procedures and trauma will be included in the study. Patients anticipated to be admitted to ICU will be excluded from the study.

Insulin treated patients will undergo BG monitoring by POC testing at bedside. A blinded Dexcom G6 will be place shortly after admission. Insulin therapy will be adjusted following POC readings (standard of care) [10,14,43]. Information on CGM readings will be collected daily during the hospital stay using the Dexcom Studio software to download the Dexcom receiver data. During the study period patients and healthcare providers will be blinded to CGM readings.

Primary and Secondary Research Outcomes:

The primary aim is difference between POC testing (standard of care) and CGM in glycemic control (efficacy outcome) and hypoglycemic and hyperglycemic events (safety outcome) during hospitalization:

1) Glycemic control, as measured by mean daily blood glucose and time in range (70-180 mg/dl)
2) Clinical significant hypoglycemia (<54 mg/dl) and severe hyperglycemia (>240 mg/dl).

Secondary outcomes include differences between groups in any of the following measures:

1. Nocturnal hypoglycemia < 70 mg/dl and < 54 mg/dl (between 22:00 and 06:00)
2. Number of hypoglycemic events (< 70 and 54 mg/dl)
3. Duration or time in hypoglycemia (minutes) during the day and night
4. Frequency and duration or time in hyperglycemia > 240 mg/dl
5. Percentage of BG readings within target BG of 70 and 180 mg/dl
6. Percentage of patients with greater than 5%-time below glucose target (<70 and 54 mg/dl)
7. Percentage of patients with greater than 5%-time above glucose target (>180 and 240 mg/dl)
8. Glycemic variability calculated by Standard Deviation, and MAGE
9. Number of sensor removal for procedures/imaging, sensors failures, sensors dislodgments
10. After discharge: time in range (TIR), frequency of and time in hypoglycemia (TIHypo), frequency of and time in hyperglycemia (TIHyper), glycemic variability (GV)
11. Accuracy of Dexcom G6 CGM, as defined by overall MARD, as compared to the standard-of-care POC and daily morning laboratory glucose values
12. Accuracy of Dexcom G6 CGM, as defined by ISO criteria (sensor values within 30/30%, 20/20%, 15/15% for values < 70 mg/dl, 70-140 mg/dl, >140-180 mg/dl and > 180 mg/dl), compared to the standard-of-care POC BG
13. Differences in accuracy between G6 CGM in the abdomen and upper arm insertion sites
14. Percentage of values within Zone A, B, C of the Clarke Error Grid

Inclusion Criteria:

1. Males and females > 18 years admitted to a general medicine or surgical service.
2. Known history of T1D or T2D receiving insulin therapy

3. Subjects must have a randomization BG between < 400 mg/dL without laboratory evidence of diabetic ketoacidosis (bicarbonate < 18 mEq/L, pH < 7.30, or positive serum or urinary ketones).
4. Patients with expected hospital length-of-stay of 3 or more days

Exclusion Criteria:
1. Patients with acute illness admitted to the ICU or expected to require admission to the ICU.
2. Patients expected to require MRI procedures during hospitalization.
3. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
4. Female subjects who are pregnant or breast‑feeding at time of enrollment into the study.

CGM Data Accuracy analysis:
Interstitial glucose values collected by CGM will be paired with POC BG (closed values within a 5 min range). Two CGM devices will be inserted– one in the abdomen and one in the upper arm- to assess differences in BG readings between upper extremity and abdominal insertion sites. In addition, patients will undergo daily venous glucose values measured by the hospital laboratory. Patients with ≥ 2 days of sensor data, and with a minimum of 70% of CGM readings over used days will be included in the comparison analysis. A minimum of approximately 70% of possible CGM readings over used days appears to generate a report that enables optimal analysis and decision-making; standard reporting and visualization of CGM data are important [44,45]. CGM metrics will include overall MARD and MAD, 30/30%, 20/20%, 10/10% for values < 70 mg/dl, 70-140 mg/dl, >140-180 mg/dl and > 180 mg/dl [45]. A three way and direct head-to-head comparison of data from the abdomen, upper arm and POC BG will be compared.

Primary Care Team (PCT) can continue to manage patients; if desired by PCT, research team can manage as follows:
Recommended Basal Bolus Insulin Protocol.
Patients will be treated with a basal bolus insulin regimen as previously reported [12,13]. The research team will follow the recommendations below to adjust insulin doses that target standard of care glycemic control goals. The primary care team will provide care concerning patients' underlying medical or surgical conditions not related to diabetes management.

TREATMENT PROTOCOL
Patients Treated with Insulin Prior to Admission
- Discontinue oral antidiabetic drugs on admission.
- Subjects treated with insulin prior to admission will receive 80% of the total daily dose (TDD) given as basal bolus regimen with basal insulin (glargine, detemir or degludec) once daily plus rapid-acting insulin (lispro or aspart) before meals.
- Half of TDD will be given as basal and half as rapid-acting insulin.
- Basal insulin will be given once daily, at the same time of the day.
- Rapid-acting insulin (lispro or aspart) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, rapid-acting insulin dose will be held.

Insulin Naïve Patients Treated with Oral Agents or GLP1-RAs Prior to Admission
- Discontinue oral antidiabetic drugs on admission.
- Starting total daily insulin dose:
  - 0.4 U/Kg/day when randomization BG between 140-200 mg/dL
  - 0.5 U/Kg/day when randomization BG between 201-400 mg/dL
  - Reduce TDD to 0.3 units per kg in patients ≥ 70 years of age and/or with a eGFR < 60 ml/min.
- Half of TDD will be given as basal insulin (glargine, detemir or degludec) once daily plus rapid-acting insulin (lispro or aspart) before meals.

- Basal insulin will be given once daily, at the same time of the day.
- Rapid-acting insulin (lispro or aspart) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, rapid-acting insulin dose will be held.

Basal Insulin adjustment.

- Daily basal (glargine, detemir or degludec) insulin dose will be adjusted as follow:
  - If the fasting and pre-dinner BG is between 100 - 140 mg/dl in the absence of hypoglycemia the previous day: no change
  - If the fasting and pre-dinner BG is between 141 - 200 mg/dl in the absence of hypoglycemia: increase basal insulin by 10% every day
  - If the fasting and pre-dinner BG is between 201 - 280 mg/dl in the absence of hypoglycemia: increase basal insulin by 20% every day
  - If the fasting and pre-dinner BG is >281 mg/dl in the absence of hypoglycemia the previous day: increase basal insulin (glargine) dose by 30% every day
  - If the fasting and pre-dinner BG is between 70 - 99 mg/dl in the absence of hypoglycemia: decrease TDD (basal and prandial) insulin dose by 10% every day
  - If BG <70 mg/dL, the insulin TDD (basal and prandial) should be decreased by 20%.
  - If BG <40 mg/dL, the insulin TDD (basal and prandial) should be decreased by 30-40%.

Supplemental insulin. Rapid-acting insulin will be administered following the "supplemental/correction insulin scale" protocol.

- If a patient is able and expected to eat most of his/her meals, supplemental insulin will be administered before meals and at bedtime following the "usual" dose of the insulin scale protocol.
- If a patient is not able to eat, supplemental insulin will be administered every 6 hours following the "sensitive" dose of the supplemental insulin scale protocol.
- **<u>Table indicates</u> number of units to be added to scheduled insulin dose.**

<u>BEFORE MEAL,</u> Supplemental Sliding Scale Insulin (number of units) - Add to scheduled insulin dose.
****Check appropriate column and cross out other columns**

BG (mg/dL)	**☐ Insulin Sensitive**	**☐ Usual**	**☐ Insulin Resistant**
< 141	No sliding scale (supplemental)insulin		
141 – 180	2	3	4
181 – 220	3	4	6
221 – 260	4	5	8
261 – 300	5	6	10
301 – 350	6	8	12
351 – 400	7	10	14
> 400	8	12	16

BEDTIME sliding scale: **Supplemental Sliding Scale Insulin dose at bedtime starting at BG > 220 mg/dL**

BG (mg/dL)	**☐ Insulin Sensitive**	**☐ Usual**	**☐ Insulin Resistant**
< 220	No sliding scale (supplemental) insulin		
221 – 260	1	2	4
261 – 300	2	3	5
301 – 350	3	4	6
351 – 400	4	5	7
> 400	5	6	8

Hospital Diabetes Education.

1. Diabetes education if not received within 1 year of admission
2. Use of glucose meters for home glucose self-monitoring
3. Keeping BG records, and will receive a logbook to record glucose tests results
4. Training on placement and care of CGM Dexcom G6
5. Hypoglycemia prevention, recognition and management

Aim 2. To determine differences in glycemic control after hospital discharge between DexcomG6 CGM and POC BG testing in hospitalized patients with diabetes.

During the hospital stay, patients will be instructed on CGM placement and care. The CGM system training sessions will be performed by a diabetes educator. The diabetes educator will educate patients on how CGM system differs from capillary SMBG, reinforcing the need for continued SMBG. Patients interested in participating in the study and willing to and able to use the CGM device will be recruited. A new CGM (blinded) will be placed in the abdomen prior to discharge. Patients will be asked to return for a clinic visit ten days after discharge to review results of BG by home POC testing. Patients will be instructed to performed POC testing before meals and bedtime. Patients with $\geq$ 2 days of sensor data, and with a minimum of 70% of CGM readings over used days will be included in the comparison analysis.

Recommendations for Insulin Discharge algorithm[12]:
Patients will be discharged following a standard protocol taking in consideration preadmission treatment (oral agents or insulin) and HbA1c value on admission as previously reported [12].

- Patients on oral agents prior to admission with an HbA1c between 7.5% and <10% will be discharged on oral agents plus basal insulin (NPH, glargine, detemir, degludec) at 50% of the daily hospital dose.
- Patients on oral agents prior to admission with an admission A1C $\geq$ 10% will be discharged on their oral agents plus basal insulin at 80% of daily hospital dose.
- Patients on oral agents plus basal insulin (NPH, glargine, detemir, degludec) prior to admission with an admission A1C between 7.5% and <10% will be discharged on their oral agents plus basal insulin at 50% of daily hospital dose.
- Patients on oral agents plus basal insulin (NPH, glargine, detemir, degludec) prior to admission with an admission A1C $\geq$ 10% will be discharged on their oral agents plus glargine U300 or glargine U100 at 80% of daily hospital dose.
- Patients treated with basal bolus regimen prior to admission will be discharged on 80% of their preadmission TDD with basal insulin once daily and rapid-acting insulin before meals.

Follow-up Care:

- New CGM (blinded) sensor will be placed in the abdomen on the day of discharge. If primary care team is planning to discharge over the weekend: participants will get new blinded sensor on Friday evening prior to discharge. Patients will be asked to return to clinic 10 days after discharge (sooner or later depending on participant's availability and schedule).
- Duration of the outpatient study is 10 days.

During follow up we will collect the following information:

1. Glycemic control:
    a. Mean daily blood glucose by CGM and POC testing
    b. Time in range (70-180 mg/dl)
    c. Frequency of overall clinically significant hypoglycemia (<54 mg/dl) and severe hyperglycemia (>240 mg/dl).
    d. Nocturnal hypoglycemia < 70 mg/dl and < 54 mg/dl (between 22:00 and 06:00)
    e. Duration or time in hypoglycemic events (minutes) during the day and night

f. Frequency and duration or time in hyperglycemia > 240 mg/dl
g. Percentage of BG readings within target BG of 70 and 180 mg/dl (time in range)
h. Percentage of patients with greater than 5%-time below glucose target (<70 mg/dl)
i. Percentage of patients with greater than 5%-time above glucose target (> 180 mg/dl)
j. Glycemic variability calculated by Standard Deviation, and MAGE

2. Diabetes treatment:
    a. Number of patients receiving insulin
    b. Insulin dosage (unit/day)
    c. Use of oral agents

3. Clinical Outcome:
    a. Hospital readmissions
    b. Emergency room visits

IV. Statistical Methods

The present study is one of two projects aimed to investigate the role of CGM (Dexcom G6 CGM) in the management of patients with diabetes in non-ICU setting receiving insulin treatment. This observational and prospective study will explore the efficacy of CGM compared to standard POC glucose testing in assessing glucose control (efficacy) and hypoglycemic events (safety) in patients with type 1 and type 2 diabetes receiving insulin during admission and after hospital discharge.

Statistical analyses will be conducted by Professor Limin Peng, PhD at the School of Public Health at Emory University. We will report baseline characteristics by hospital service (medicine and surgery), diabetes type (T1D and T2D), and risk factors for hypoglycemia. The rates of incidence of hypoglycemia will be calculated based on the data obtained by CGM and POC. Comparisons will be made with the use of Wilcoxon tests (or Kruskal– Wallis tests) and Chi-square tests (or Fisher's exact test) as appropriate. Multivariate linear regression will be conducted to assess the difference in continuous secondary outcomes between the two groups while other relevant covariates. To be eligible for analysis at least 70% of CGM values need to be available per day, with at least 2 eligible days of data per subject in each study arm (inpatient and outpatient). Glucose patterns will be analyzed based on the Ambulatory Glucose Profile, recently endorsed by an international expert as a standardized approach for CGM interpretation [44]. Hospital glucose values after the first day of insulin treatment will be included in the analysis to allow us to have a full 24-hrs glucose profile and to avoid analyzing day-1 CGM values which may have lower accuracy. For clinical accuracy, CGM and POC BG will be paired and will be plot in the Clarke Error Grid [46,47]. Paired CGM and POC BG falling in the Zone A will be defined as "accurate", and in Zone B as "acceptable", with remaining values considered "not acceptable" if falling in Zone C, D, or E.

A total of 105 (first five randomized subjects will not be included in the statistical analysis, instead, we will review any potential issues with recording/downloading data from their sensors to troubleshoot any possible problems with the software) insulin treated patients will be included in this prospective observational study. Based on previous studies by our unit, we anticipate that 80% of patients will complete the inpatient and ambulatory arms of the study [13,48].

V. Methods and Procedures Applied to Human Subjects:

Potential Risk to Human Subjects

Hypoglycemia. The risk of hypoglycemia in non-ICU patients treated with basal-bolus insulin is between 12%–35% [14,19,37,49]. In this analysis, hypoglycemia is defined as a BG or IG < 70 mg/dL. Clinical significant hypoglycemia is defined as BG or IG < 54 mg/dl. Severe hypoglycemia is defined as BG or IG < 40 mg/dL.

Use of CGM. No major risks are expected with the use of the CGM device. Pain and bleeding with insertion is minimal. Skin irritation may occur in those sensitive to adhesives. Other potential risks and drawbacks of using CGM described in the literature including unrealistic expectations, overly-aggressive correction of elevated glucose levels, and alerts and alarms won't be an issue in this study because we will use blinded CGM.

Protection against Risks

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor capillary BG at the bedside using a hand-held glucose meter, b) only experienced nurses/or phlebotomist will draw blood samples, and c) women of reproductive age who are sexually active will undergo a urine pregnancy tests prior to participation in the study. To prevent significant clinical events, no patients with history of significant liver, renal impairment or cardiac failure will be recruited in this study.

We expect that approximately 10% in the inpatient setting and ~20% in the outpatient (post-discharge) arm will experience one or more episodes of hypoglycemia. To minimize the risk of hypoglycemia, the starting dose will be reduced in the basal bolus insulin regimen (TDD: 0.4 units per kg of body weight), in addition, in patients ≥ 70 years of age and/or eGFR < 60 ml/min the TTD will be further reduce to 0.3 units/kg. To avoid hypoglycemia, the total daily dose of insulin will be decreased by 10% for BG between 70-99 mg/dl and by 20% after each episode of hypoglycemia (BG < 70 mg/dl). In addition, in patients treated with insulin at home, the TDD of insulin will be reduced by 20% on admission and the attending physician may further reduce insulin dose in the presence of severe hypoglycemia.

Hypoglycemia will be treated with dextrose infusion. Dextrose 50% solution will be given for glucose values < 70 mg/dl. If the patient is awake, 25 ml (1/2 amp) will be given IV or oral juice/snack (crackers) as per protocol. If the patient is not awake: 50 ml (1 amp) will be given STAT. Blood glucose levels will be repeated in 15 minutes and dextrose administration will be repeated as needed for values < 70 mg/dl.

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.

Recruitment and Consent. Coordinators will screen for potential participants from the electronic medical record. Subjects will be provided with sufficient information on the practice of glucose monitoring before providing written consent. The process of obtaining informed consent will follow the standard procedures of Emory University. This protocol will be submitted for approval by the Emory IRB.

Potential Benefits to Human Subjects. Subject participating in this trial will not receive any direct benefits during the hospital stay, since treatment decision will be made based on POC BG (standard of care). In the discharge follow up, investigators will analyze glucose profiles in a more detailed manner with potential for better treatment modifications in the future.

Inclusion of children. No patients under the age of 18 will be recruited in this study.

Confidentiality. Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important and key points of the study. One of the investigators or research coordinators will obtain a witnessed informed consent prior to inclusion of a patient into the study. Data collection records with personal identifiers will be stored in locked file cabinets. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, coordinators and the IRB at Emory University.

Payment for Participation. Participation in this study is voluntary. Patients will receive one hundred dollars ($100.00) during the hospital stay and fifty dollars ($50.00) at the follow up visit 10 days after discharge. Total

compensation will be one hundred and fifty dollars ($150). Transportation to outpatient clinic visit will be arranged for those who need transportation.

Financial Obligation. No additional cost to patients or to the institution will be incurred for research purposes. Research studies will be performed at no cost to study subjects. CGM will be provided by the sponsor at no cost to participants.

Research Injuries. If a patient is injured because of taking part in this study, Dr. Umpierrez and investigators, along with the medical facility will make medical care available to the patient at the patient's own cost. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

Financial Conflict of Interests. None of the investigators in this study have any outside activities that may represent a conflict of interest. None of the investigators have an economic interest in an outside entity, or act as officers, directors, employees or consultants with such an entity, whose financial interest may be affected by this research study.

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

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