Scripps Digital Diabetes – Glucose as a Vital Sign
A translational and transformational digital diabetes care program

Managing type 1 and high risk type 2 diabetes in the hospital setting

Study sites:	Scripps Whittier Diabetes Institute and Scripps Health
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Sponsor:	Scripps Whittier Diabetes Institute
Version:	January 9th, 2020

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Protocol Synopsis

Title:	**Scripps Digital Diabetes – Glucose as a Vital Sign** Managing type 1 and high risk type 2 diabetes in the hospital setting
Study sites:	Scripps Whittier Diabetes Institute and all Scripps Health hospitals
Sponsor:	Scripps Whittier Diabetes Institute
Investigational Device:	Dexcom G6, Investigation Use Only (IUO) Continuous Glucose Monitoring (CGM) System (the "IUO CGM")
Pilot Study Design and Sample Size:	Pilot Type 1 observational study – 5 patients Type 2 randomized study – 56 patients
Pilot Expected Completion Date:	5 months from 1st patient enrolled
Study Design and Sample Size (randomization based on statistical analysis):	Type 1 observational study – 100 patients Type 2 randomized study – 404 patients, Subset using Dexcom G6, n=110 patients for full evaluation and analysis.
Expected Completion Date:	5 years from 1st patient enrolled

Purpose:

This program will provide patients with type 1 and high risk type 2 diabetes the safest hospitalization by using wireless continuous glucose monitoring devices (CGM) to track their glucose parameters in real-time similar to other continuously monitored vital signs. The CGM will inform a team of health professionals who will monitor the patients' progress, communicate recommendations, and be available for discussion when recommended targets are not achieved. Health teams will utilize sensor results in addition to existing electronic medical records data to evaluate progress and manage care.

Inclusion Criteria:

1. 18 years of age and above
2. One of the following:
   a. Diagnosed with diabetes type 1 OR
   b. Diagnosed with diabetes type 2, requiring insulin during this hospitalization, and any of the following:
      I. HbA1c > 8%
      II. Point-of-care blood glucose (POC) > 180 mg/dL at admission.
      III. Point-of-care blood glucose tests (POC) > 200 mg/dL or chemistry glucose >200 mg/dl on at least three different time points within the last 24 hours, before consenting.
   c. English or Spanish speaker.

Exclusion Criteria:

1. Pregnant
2. Patient in ICU and with insulin drip (participants in ICU not on the insulin drip are allowed)
3. Known allergy to adhesives
4. Anticipated CT/MRI/diathermy procedure within 24 hours from admission (patients with a planned operation within 24 hours from admission may be included in the study before the operation – see Sensor Insertion/Transmitter Connection section of the protocol).
5. Current participation in any medication or device research study
6. Have any condition that in the opinion of the Principal Investigator is deemed contraindicated for study participation

Overview:

All patients with type 1 or type 2 diabetes who meet study criteria will be invited to participate in the study. All patients included in the study will be followed by an advanced practice diabetes nurse (APN) for glucose management during their hospitalization. All patients included in the study will receive a CGM. Patients with type 2 diabetes will be randomized to control (blinded CGM glucose values) or intervention (CGM blood glucose values will be used to aid with glucose management during the hospitalization). In addition, a research only supplemental order set will be implemented for all study participants. The order set focuses on any glucose point of care test that is between 70-79 mg/dL at any time or ≥ 201 mg/dl at night, between 9pm and 4am (21:00-04:00). (Appendix B). The goal is to prevent hypoglycemia and hyperglycemia for all study patients. The advanced practice diabetes nurse will work with the physician in charge of the patient's care as well as the patient's care team.

Patients with type 1 diabetes:

Patients with type 1 diabetes will receive a CGM. The CGM device will be placed for the length of the patient's stay with sensor changes at 240 hours (10 days) post insertion or as needed. Calibrations are not required for the IUO CGM and will not be performed routinely.
The CGM device will be kept unblinded, which means that the data can be viewed at the patient's bedside. Monitoring devices will be set to alarm if rate of change is trending towards hypoglycemia with a value of ≤ 90 mg/dL or trending towards severe hyperglycemia with a value of ≥ 250 mg/dL. Wireless communication will allow for assigned personnel to view CGM values at real time and also be alerted by alarms set by specifications above. Nursing staff assigned to the patient will then conduct POC testing. If the initial POC testing value after alarm is 70-79 mg/dL then the patient will receive 15 gm glucose gel with follow up POC testing per APN recommendations, based on supplemental order set (PFO). Below 70mg/dl, patients are treated based on established hypoglycemia standing orders. If the initial POC testing value after alarm is ≥ 201 mg/dL then insulin adjustments will be individualized based on the patient's clinical scenario. Patients receive supplemental insulin for hyperglycemia only if POC testing ≥ 201mg/dl is between 9pm and 4am (21:00-04:00) and they have not received any additional insulin for the past three hours. Thereafter, follow up POC testing will continue according to APN recommendations. In addition, insulin adjustment algorithms will be used by the APN after CGM and POCT values ongoing daily review and communication with the physician and care team, to maintain glucose levels within goal. Communication between glucose management team, nursing staff and monitoring physician may take place more often if trends towards hypoglycemia or hyperglycemia are visible.

CGM data will automatically be uploaded to a commercially available, web-based service (Dexcom ClarityTM Diabetes Management Software) using the Scripps' wifi connection. This system enables research staff to review historical CGM data and also provides summary reports, including average glucose and patterns of high and low glucose.

POC glucose values, HbA1c level at admission and usual care laboratory glucose values will be collected as well. A follow-up questionnaire will take place within 7 days from discharge (including discharge date) to assess any adverse events and to obtain patient satisfaction data regarding his/her hospital stay and use of the CGM device.

For data analysis, the percentage of patient-days with average glucose within 70-180 mg/dL will be compared to historical baseline data.

Patients with type 2 diabetes:

All type 2 patients enrolled will receive the CGM device, but patients will be randomized to control (CGM glucose values are blinded to APN, care team and researchers) or intervention (CGM blood glucose values will be used to aid with glucose management during the hospitalization). CGM data will be compared between both groups during data analysis. CGM data will be blinded for all type 2 patients. This means that data will not be viewed at the patient's bedside, but will be reviewed remotely by research staff for the intervention group. In short, the CGM device will be placed for the length of the patient's stay with sensor changes at 240 hours (10 days) post insertion or as needed. Calibrations are not required for the IUO CGM and will not be performed routinely.

For the intervention group, monitoring devices will be set to alarm remotely if rate of change is trending towards hypoglycemia with a value of ≤ 90 mg/dL or trending towards severe hyperglycemia with a value of > 250 mg/dL. Wireless communication will allow for assigned personnel to view CGM values at real time and also be alerted by alarms set by specifications above. Nursing staff assigned to the patient will then conduct POC testing. If the initial POC testing value after alarm is 70-79 mg/dL then the patient will receive 15 gm glucose gel with follow up POC testing per APN recommendations, based on supplemental order set (PFO). Below 70mg/dl, patients are treated based on established hypoglycemia standing orders. If the initial POC testing value after alarm is ≥ 201 mg/dL then insulin is administered in accordance with supplemental research order set. Patients receive supplemental insulin for hyperglycemia only if POC testing ≥201 mg/dl is between 9pm and 4am (21:00-04:00) and they have not received any additional insulin for the past three hours. In addition, APNs will recommend insulin adjustments based on daily review of CGM trends and POCT values. Communication between glucose management team, nursing staff and monitoring physician may take place more often if trends towards hypoglycemia or hyperglycemia are visible.

CGM data will automatically be uploaded to a commercially available, web-based service (Dexcom ClarityTM Diabetes Management Software) using the Scripps' wifi connection. This system enables research staff to review historical CGM data and also provides summary reports, including average glucose and patterns of high and low glucose.

POC glucose values, HbA1c level at admission and usual care laboratory glucose values will be collected for both control and intervention groups. A follow-up questionnaire will take place within 7 days from discharge (including discharge date) for both groups to assess any adverse events, patient satisfaction with hospital stay and patient satisfaction regarding the use of the CGM device.

Patients who are randomized to the control group may still benefit from study participation as the research only supplemental order set will be used for this group as well with the goal of preventing

hypo and hyperglycemia. The control group may also benefit from the daily visits from the research staff as diabetes education would be provided for all.

For data analysis, the percentage of patient-days with average glucose within 70-180 mg/dL will be compared between both groups.

Study Aims:

Aim 1 (observational): To compare the percentage of patient-days with average glucose in the target range (70-250 mg/dL) among patients with type 1 diabetes receiving CGM versus historical baseline data.

Aim 2: To compare the percentage of readings in the target range (70-250 mg/dL) among patients with type 2 diabetes randomized to control versus intervention.

Aim 3: To examine the acceptability and feasibility of using CGM in the hospital environment from patient (type 1 and type 2 diabetes) and provider perspectives.

Aim 4 (exploratory): To compare rates of hypoglycemia (<70 and < 54 mg/dL) and hyperglycemia (>180mg/dL, >250 and 300 mg/dL) among patients with type 1 diabetes receiving CGM versus historical baseline data.

Aim 5 (secondary/exploratory): To compare rates of hypoglycemia (<70 and < 54mg/dL) and hyperglycemia (>250 and 300 mg/dL) among patients with type 2 randomized to control versus intervention.

Statistical Analysis Plan (SAP); see full plan in Appendix C:

All patients with type 1 diabetes will receive CGM (CGM data used for glucose management). This is an observational aspect of the study with no further analysis.

See SAP in Appendix C for plan for type 2 diabetes analysis.

Protocol

Background

People with type 1 diabetes make up a small portion of hospital admissions annually but when hospitalized with critical medical conditions blood glucose values can fluctuate dramatically, quickly putting patients at risk for complications of hyperglycemia and severe hypoglycemia (1-10). People with type 2 diabetes who use insulin or are at high risk of complications with uncontrolled hyperglycemia are also at increased risk in the hospital setting. A study by Mendez et al. indicated that glucose variability in non-critically ill patients in the hospital setting was associated with longer length of stay and increased number of deaths over a 90 day period (11). Optimally, in an acute care setting blood glucose monitoring should occur continuously, similar to other vital signs such as heart rate, heart rhythm, oxygen levels and blood pressure. Hyper and hypo-glycemia can be prevented by ongoing monitoring of trends and changes in blood glucose values and immediate intervention when values rise above or fall below the target ranges. Moreover, unwanted complications related to fluctuations in blood glucose will be prevented with frequent monitoring and management that maintains normoglycemia.

There are several continuous glucose monitoring (CGM) devices available in the ambulatory care setting that allow rapid, real-time monitoring of patients' subcutaneous interstitial fluid glucose values and provide a warning system to people with diabetes that glucose values may be or will likely be entering dangerous levels. Currently there are no subcutaneous CGM devices approved for use in the United States for a hospital environment. These devices offer an accurate display of glucose values and trends with high and low alarms. Additionally, a new app allows wireless transmission of glucose values to a central location for monitoring. This is similar to the telemetry units found in hospitals that monitor ongoing heart rate and rhythm. Studies using similar devices in acute care environments in Europe and South America have demonstrated clinical and economic success by maintaining glucose control within target ranges and improving health cost outcomes by decreasing staff time required for point of care monitoring and shortening length of hospital stay. (12-14)

Specific Aims

We hypothesize that instituting the broad use of subcutaneous CGM with wireless transmission to an advanced practice diabetes team for high risk patients with type 1and type 2 diabetes will result in improved well-managed glucose days, fewer episodes of severe hyper- and hypoglycemia, and improved patient satisfaction. We propose using existing subcutaneous CGM technology to monitor rapid, real-time glucose values in patients admitted to a Scripps hospital to determine the effectiveness of maintaining normoglycemia and reducing rates of hyper- and hypoglycemia and to evaluate patient and provider satisfaction with using this device in a hospital environment. All patients included in the study will be followed by an advanced practice diabetes nurse for glucose management during their hospitalization. All patients included in the study will receive a CGM. Patients with type 2 diabetes will be randomized to control (blinded CGM glucose values to APN,

care team and researchers) or intervention (CGM blood glucose values will be used to aid with glucose management during the hospitalization). In addition, a research only supplemental order set will be implemented for all study participants. The order set focuses on any glucose point of care test that is between 70-79 mg/dL at any time or ≥ 201 mg/dl at night, between 9pm and 4am (21:00-04:00). The goal is to prevent hypoglycemia and hyperglycemia for all study patients. The advanced practice diabetes nurse will work with the physician in charge of the patient's care as well as the patient's care team. Historical baseline data for type 1 diabetes patients will be used as comparison for Aim 1 and Aim 4 below. Historical baseline data is defined as patients with type 1 diabetes admitted to a Scripps hospital within 24 months before first patient enrolled.

Aim 1 (observational): To compare the percentage of patient-days with average glucose in the target range (70-250 mg/dL) among patients with type 1 diabetes receiving CGM versus historical baseline data.

Aim 2: To compare the percentage of readings in the target range (70-250 mg/dL) among patients with type 2 diabetes randomized to control versus intervention.

Aim 3: To examine the acceptability and feasibility of using CGM in the hospital environment from patient (type 1 and type 2 diabetes) and provider perspectives.

Aim 4 (exploratory): To compare rates of hypoglycemia (<70 and < 54 mg/dL) and hyperglycemia (>180mg/dL, >250 and 300 mg/dL) among patients with type 1 diabetes receiving CGM versus historical baseline data.

Aim 5 (secondary/exploratory): To compare rates of hypoglycemia (<70 and < 54 mg/dL) and hyperglycemia (>250 and 300 mg/dL) among patients with type 2 randomized to control versus intervention.

Secondary analyses will examine additional parameters derived from CGM data (e.g., measures of central tendency, variability indicators, time spent within/outside target ranges).

Study sites

Although type 1 diabetes is not always well documented in the hospital environment we estimate that there are 1000-1500 admissions per year with type 1 diabetes to the Scripps hospitals countywide. Scripps has four licensed hospitals at five locations throughout San Diego County which range from the border of Mexico with Scripps Mercy Chula Vista to south of Camp Pendleton with Scripps Memorial Encinitas. There are three additional central and coastal locations with Scripps Mercy San Diego, Scripps Memorial La Jolla and Scripps Green. The hospitals serve a diverse ethnic and socioeconomic population of patients with type 1 and type 2

diabetes. In 2012, there were 412 admissions for diabetic ketoacidosis, a life threatening condition which occurs almost exclusively in type 1 diabetes. In the same year, there were 12,000 admissions for patients with type 2 diabetes. The ability to monitor blood glucose continuously in high risk diabetes patient populations would allow safer and more rapid resolution of hyperglycemia while preventing adverse events of hypoglycemia.

Patients with type 1 diabetes will be recruited at any Scripps hospital site (main sites will be La Jolla, Mercy San Diego, Green and Chula Vista as staffing permits). Patients with type 2 diabetes will be recruited mainly at Scripps Mercy Chula Vista and Scripps Mercy San Diego where their mean length of stay is 7 days within the Medical/Surgical units. Patients may also be recruited at other Scripps hospital sites.

Inclusion Criteria:

1. 18 years of age and above
2. One of the following:
   a. Diagnosed with diabetes type 1 OR
   b. Diagnosed with diabetes type 2, requiring insulin during this hospitalization, and any of the following:
      I. HbA1c > 8%
      II. Point-of-care blood glucose (POC) > 180 mg/dL at admission
      III. Point-of-care blood glucose tests (POC)> 200 mg/dl or chemistry glucose >200 mg/dL on at least three different time points within the last 24 hours, before consenting.
3. English or Spanish speaker

Exclusion Criteria:

1. Pregnant
2. Patient in ICU and with insulin drip (participants in ICU not on the insulin drip are allowed)
3. Known allergy to adhesives
4. Anticipated CT/MRI/diathermy procedure within 24 hours from admission (patients with a planned operation within 24 hours from admission may be included in the study post operation – see Sensor Insertion/Transmitter Connection section of the protocol).
5. Current participation in any medication or device research study
6. Have any condition that in the opinion of the Principal Investigator is deemed contraindicated for study participation

Study Design

We will conduct a study to test the feasibility and utility of providing CGM monitoring devices to each of the Scripps hospitals for use when patients aged 18 and above with type 1 or high risk type 2 diabetes are admitted to the general wards or step-down units over a 2 year time period. Patients with type 1 or type 2 diabetes will be identified at the time of admission by the emergency department, admitting nurse or attending physician. Patients with diabetes type 1 or 2 will undergo chart review to determine if they meet study inclusion/exclusion criteria. Scripps staff will be trained to notify the hospital glucose management team for all admissions of type 1 or type 2 diabetes.

All patients included in the study will be followed by an advanced practice diabetes nurse for glucose management during their hospitalization. The advanced practice diabetes nurse will work with the physician in charge of the patient's care as well as the patient's care team.

Licensed clinical staff will perform daily evaluation of CGM insertion site. Research staff will be available to respond to any questions patient and/or hospital staff may have concerning study and CGM.

Patients with type 1 diabetes:

Patients with type 1 diabetes will receive a CGM. The CGM device will be placed for the length of the patient's stay with sensor changes at 240 hours (10 days) post insertion or as needed. Calibrations are not required for the IUO CGM and will not be performed routinely.
The CGM device will be kept unblinded, which means that the data can be viewed at the patient's bedside. Monitoring devices will be set to alarm if rate of change is trending towards hypoglycemia with a value of ≤ 90 mg/dL or trending towards severe hyperglycemia with a value of ≥ 250 mg/dL. Wireless communication will allow for assigned personnel to view CGM values at real time and also be alerted by alarms set by specifications above. Nursing staff assigned to the patient will then conduct POC testing. If the initial POC testing value after alarm is 70-79 mg/dL then the patient will receive 15 gm glucose gel with follow up POC testing per APN recommendations, based on supplemental order set (PFO). Below 70mg/dl, patients are treated based on established hypoglycemia standing orders. If the initial POC testing value after alarm is ≥ 201 mg/dL then insulin adjustments will be individualized based on the patient's clinical scenario. Patients receive supplemental insulin for hyperglycemia only if POC testing ≥ 201mg/dl is between 9pm and 4am (21:00-04:00) and they have not received any additional insulin for the past three hours.. Thereafter, follow up POC testing will continue according to APN recommendations. In addition, insulin adjustment algorithms will be used by the APN after CGM and POCT values ongoing daily review and communication with the physician and care team, to maintain glucose levels within goal. Communication between glucose management team, nursing

staff and monitoring physician may take place more often if trends towards hypoglycemia or hyperglycemia are visible.

If a patient arrives to the hospital with a CGM device, it will be discontinued and a new study sensor, transmitter and CGM device will be used.

CGM data will automatically be uploaded to a commercially available, web-based service (Dexcom ClarityTM Diabetes Management Software) using the Scripps' wifi connection. This system enables research staff to review historical CGM data and also provides summary reports, including average glucose and patterns of high and low glucose.

POC glucose values, HbA1c level at admission and usual care laboratory glucose values will be collected as well. A follow-up questionnaire will take place within 7 days from discharge (including discharge date) to assess any adverse events and to obtain patient satisfaction data regarding his/her hospital stay and use of the CGM device.

For data analysis, the percentage of patient-days with average glucose within 70-180 mg/dL will be compared to historical baseline data where available.

Patients with type 2 diabetes:

All type 2 patients enrolled will receive the CGM device, but patients will be randomized to control (CGM glucose values are blinded to APN, care team and researchers) or intervention (CGM blood glucose values will be used to aid with glucose management during the hospitalization). CGM data will be compared between both groups during data analysis. CGM data will be blinded for all type 2 patients. This means that data will not be viewed at the patient's bedside, but will be reviewed remotely by research staff for the intervention group. In short, the CGM device will be placed for the length of the patient's stay with sensor changes at 240 hours (10 days) post insertion or as needed. Calibrations are not required for the IUO CGM and will not be performed routinely.

For the intervention group, monitoring devices will be set to alarm remotely if rate of change is trending towards hypoglycemia with a value of $\leq$ 90 mg/dL or trending towards severe hyperglycemia with a value of $\geq$ 250 mg/dL. Wireless communication will allow for assigned personnel to view CGM values at real time and also be alerted by alarms set by specifications above. Nursing staff assigned to the patient will then conduct POC testing. If the initial POC testing value after alarm is 70-79 mg/dL then the patient will receive 15 gm glucose gel with follow up POC testing per APN recommendations, based on supplemental order set (PFO). Below 70mg/dl, patients are treated based on established hypoglycemia standing orders. If the initial POC

testing value after alarm is ≥201 mg/dL then insulin adjustments will be individualized based on the patient's clinical scenario. Patients receive supplemental insulin for hyperglycemia only if POC testing ≥201mg/dl is between 9pm and 4am (21:00-04:00) and they have not received any additional insulin for the past three hours.. Thereafter, follow up POC testing will continue according to APN recommendations. In addition, insulin adjustment algorithms will be used by the APN after CGM and POCT values ongoing daily review and communication with the physician and care team, to maintain glucose levels within goal. Communication between glucose management team, nursing staff and monitoring physician may take place more often if trends towards hypoglycemia or hyperglycemia are visible.

CGM data will automatically be uploaded to a commercially available, web-based service (Dexcom ClarityTM Diabetes Management Software) using the Scripps' wifi connection. This system enables research staff to review historical CGM data and also provides summary reports, including average glucose and patterns of high and low glucose.

POC glucose values, HbA1c level at admission and usual care laboratory glucose values will be collected for both control and intervention groups. A follow-up questionnaire will take place within 7 days from discharge (including discharge date) for both groups to assess any adverse events, patient satisfaction with hospital stay and patient satisfaction regarding the use of the CGM device.

Patients who are randomized to the control group may still benefit from study participation as the research only supplemental order set will be used for this group as well with the goal of preventing hypo and hyperglycemia. The control group may also benefit from the daily visits from the research staff as diabetes education would be provided for all.

For data analysis, the percentage of patient-days with average glucose within 70-180 mg/dL will be compared between both groups.

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Materials and Methods

Device overview (POCT equipment)

Used hospital wide. Any POC test done for study purposes only (per CGM alarms) will be coded separately for easier access for study data purposes. This equipment is calibrated on a daily basis and will not function if a calibration has not taken place within the last 24 hrs.

Device overview (Sensor applicator/Sensor)

Dexcom G6 IUO CGM Sensor

The applicator is molded so that insertion of the needle occurs at a 45 degree angle. The applicator includes a built-in sensor. Sensor insertion occurs in one step, by pressing button. The sensor pod remains on the skin with the sensor probe (platinum/silver wire) below the skin.

Device overview

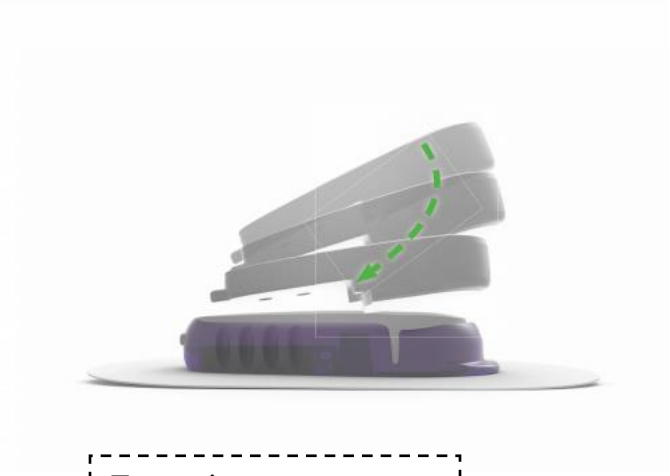
[Information from IUO CGM Investigator Brochure]

Transmitter

The transmitter is designed to continuously measure the electrochemical signal produced by the sensor probe. It can be re-used for multiple sessions. The transmitter is worn over the sensor and secured within the transmitter holder after the sensor is deployed by the auto-applicator.

The transmitter is programmed with a specific Identification Number (ID) which must be entered into the mobile app to establish a secure Bluetooth wireless communication between the devices, and allow for the following features to be available: display of real-time glucose information; glucose-related alerts or alarms; indicators of "failsafe" mechanisms that the sensor cannot provide meaningful glucose information, such as signal loss, the end of the sensor session, and ability to connect to Dexcom Share Service or Dexcom CLARITYTM Diabetes Management Software.

Once the glucose monitoring session is initiated, the transmitter does not require calibration entries.



Transmitter

Mobile Application

Mobile app (on Phone) communicates with the transmitter via Bluetooth and displays glucose information in real-time. The IUO CGM System requires a two-hour warm up period after which it will display data once every five minutes for up to ten days.

The mobile application has a menu setting for glucose related alerts and alarms. High and low glucose alerts can be set to warn against glucose excursions. The mobile application also provides a low glucose alarm set at 55 mg/dL. In addition to glucose excursions, additional alerts can be configured, including predictive alerts (Action Alert) for warning users of impending low glucose of 55 mg/dL, signal loss, the end of the sensor session, or the need to calibrate.

In addition to displaying real time glucose data and alerts to users, the mobile app provides connectivity to the Dexcom Share Service offering the ability to share their CGM data wirelessly with up to five individuals. Once the Share feature in the mobile app is activated, the mobile device transfers glucose readings to the Dexcom Share Cloud using either Wi-Fi or a cellular data plan. The sensor glucose readings are then sent from the Dexcom Share Cloud to the mobile device of the Follower, the person remotely monitoring the user's glucose, via Wi-Fi or cellular data.

Sharer and Follower equipment

The Dexcom IUO CGM transmitter can directly transmit blood glucose readings to compatible phones. A phone will therefore be placed at patient's bedside. Phones will have multiple functions: receive blood sugar values, upload these values automatically (via wifi) to Clarity™, store blood sugar values for up to 30 days (for the event that wifi connection is temporarily lost) and lastly can send values to selected followers.

Type 2 Patients: These patients are blinded to their blood glucose readings. Phone will be stored in a box at bedside. Depending on whether patient is in intervention or control group, phone will accordingly transmit data to selected followers or not.

Type 1 patients: These patients can see their blood glucose readings. Phone will be given to them while in study, in order to see their blood sugar values.

A compatible device (Android, iPhone or iPad) will be used by the follower (assigned research staff and/or telemetry unit) to view all CGM data.

Security of equipment

The phone will remain at the participant's bedside until discharge. The CGM Share Direct allows for mobility and will follow the patient as able, as an extension to the IV pole. The equipment will be enclosed in a secured container that will allow access from study staff as needed.

CGM data will automatically be uploaded to a commercially available, web-based service (Dexcom Clarity™ Diabetes Management Software) using the Scripps' wifi connection. This

system enables research staff to review historical CGM data and also provides summary reports, including average glucose and patterns of high and low glucose.

The Dexcom Studio application as well as IBM SPSS (a statistical package) will be used for data analysis.

Cleaning of Devices

The sensor applicator as well as the sensor itself are disposable after each use. The transmitter, phone and share station will be transferred to other study participants after thorough cleaning and disinfecting between patients (following Scripps wide cleaning/disinfecting instructions [applicable to POC equipment as well] Appendix A). As part of this study we will be applying the same transferability between patients as with the Professional System following thorough cleaning and disinfecting steps.

Study Procedures

Informed Consent

The consent form provided will be available in English and Spanish (consent forms will be translated by certified translators). The research staff, which includes the research nurse, diabetes educator or diabetes advance practice nurse, fluent in Spanish and English, will conduct the consenting process in the participants' preferred language. The research staff will ensure that participants understand all information provided, answer participants' questions and concerns, and inform them that their participation is completely voluntary and will in no way affect their relationship with Scripps Health. The research staff will provide participants a copy of their signed form. A participant will not be excluded if illiterate or if he/she has visual problems (this may include recent procedures to the eye/s, which is a common finding for patients with advanced diabetes disease). A participant will not be included if legally blind at both eyes or if primary reading ability is thru braille. A witness line will be used for a third person to sign (the person must be fluent in English or Spanish, the language of the participant). As above, the research staff will ensure that the witness as well, understands all information provided.

All research staff has completed the CITI Human Subjects Training and under the direction of the nurse research coordinator, have also received extensive training on obtaining study consent. They will review all sections of the consent form and ensure that the potential participant comprehends the information provided and is capable of making an informed choice to participate. Consent forms will be stored in locked cabinets at the Scripps Whittier Diabetes Institute, separate from all

other study data to ensure the confidentiality of any information that participants disclose. Consent forms will be kept for six years at which point they will be shredded.

Screening and Enrollment:

Patients with type 1 or type 2 diabetes will be identified during their hospitalization by Research staff, by using the daily hospital reports of abnormal blood sugars for all hospitalized patients. Patients with diabetes type 1 or 2 will undergo chart review to determine if they meet study inclusion/exclusion criteria.

Once a patient is determined to meet study criteria, the physician in charge of the care of the patient while hospitalized, will be contacted to approve patient inclusion in the study. If patient and physician are in agreement, the consent process will proceed.

A patient can only participate once in the event of multiple hospitalizations.

A screening list will be kept of all patients who are approached for study participation. These lists will be kept until the end of study enrollment period.

Post screening procedures: After consent signing and before sensor insertion

The following post screening procedures will take place within 7 days before sensor insertion. These procedures include: Collection of medical/diabetes history, vital signs, height, weight, HbA1c, hematocrit. The following post screening procedure will take place within 72 hrs before sensor insertion: Pregnancy test and evaluation of sensor insertion area (integumentary system at abdomen,).

All these procedures are part of the usual hospital procedures for patient care. No post screening procedures will be done solely for study purposes. All data from these procedures will be kept for study purposes.

Sensor Insertion/Transmitter Connection:

Once a patient has met all inclusion/exclusion criteria, signed consent, and completed the post screening procedures, he/she will have a sensor placed (see Device overview section above). The placement of the sensor will be done by the diabetes research nurse, the RN diabetes educator or the diabetes advance practice nurse (RN or RD).

Basic metabolic panel values will be collected +/- 24 hours before sensor insertion. These values are part of usual patient care. Any diabetes medications, acetaminophen and steroid use within the last 24 hours before sensor insertion will be documented as well as pre-insertion vital signs. The insertion site will be cleaned with alcohol swabs, the sensor will be placed and subsequently the transmitter will be connected for communication of data to the phone. The phone will be maintained up to a maximum of 20 feet away for the patient.

If the patient is to have a surgical procedure and the patient has been consented, then solely the sensor can be placed. The initial accuracy of CGM data is based on the length of time the sensor is in place and the CGM data has been shown to increase in accuracy with continued sensor wear. After the surgical procedure, the transmitter will be connected for communication of data to the receiver.

Sensor and transmitter will be removed before any CT, MRI or surgery. After procedure is complete, a new sensor can be placed if patient agrees.

Glucose Management

An Inpatient Glycemic Management Advanced Practice Registered Nurse Standardized Procedure (APN-S) will be followed (Appendix B: supplemental order set for subcutaneous insulin or PFO). The standardized procedure uses specific guidelines for the management of patients with diabetes within the hospital setting. The target goal for in-hospital blood glucose values are pre-prandial BG of 100-140 mg/dL and random BG less than 180 mg/dL.

Per PFO, if the initial POC testing value after alarm is 70-79 mg/dL then the patient will receive 15 gm glucose gel with follow up POC testing within 15 minutes. If the initial POC testing value after alarm is ≥ 201 mg/dL anytime between 9pm (21:00) and 4am (04:00), and the patient has not received any insulin over the past three (3) hours, then patient will receive supplemental insulin dose, which is based on patient's current order of correction insulin. Communication will be ongoing between the advanced practice diabetes team, physician in charge of the patient's care as well as the patient's care team.

For Type 1 patients or Type 2 patients randomized in Intervention group, , CGM data will be used by APN to evaluate BG control of the patient every 24 hrs and/or earlier based on alarm CGM settings and rates of change arrows. The CGM device will be set to alarm if rate of change is trending towards hypoglycemia with a value of ≤ 90 mg/dL (arrow being shown will be  , which means that if BG continues falling at this rate, BG could decrease up to 30 mg/dL in 15 minutes) or trending towards severe hyperglycemia with a value of ≥ 250 mg/dL (arrow being shown will be , which means that if BG continues rising at this rate, BG could increase up to 30 mg/dL in

15 minutes). Trend arrows (rising, rapidly rising and falling and rapidly falling), will be taken into consideration looking at the whole patient picture, including nutritional intake and timing of meals/medications. When CGM alarms, "Followers" (which may include research staff and/or tele tech staff) will alert nursing staff assigned to the patient to conduct POC testing and treat patient accordingly per Research (PFO) or Hospital protocol (whichever applies).

For Type 2 patients randomized to the Control group, blood glucose values from CGM are not visible by APN or tele tech staff. PFO will still apply during any time patient gets a POC from bedside RN per standard hospital procedures.

Sensor Removal:

The sensor will be removed before hospital discharge, at day 10 post insertion, if the sensor fails for any reason or if the patient is to undergo a CT or MRI procedure. The sensor may also be removed at the discretion of the Principal Investigator. If the patient is to continue hospitalization, then a new sensor will be inserted. Once a sensor is removed, the insertion site will be examined for any inflammation/bleeding.

Follow-up:

A follow-up questionnaire will take place within 7 days from discharge (including discharge date) to assess any adverse events and to obtain patient satisfaction data regarding his/her hospital stay and use of the CGM device.

Provider satisfaction data will also be gathered (via focus group or questionnaire) after study patients have been discharged.

Measurements and Analysis

Clinical measures: Clinical measures that will be collected will include HbA1c on admission and at any time post admission while the patient is hospitalized, point of care glucose values conducted with the hospital based glucose meters (a minimum of four times a day) and CGM downloaded data. The reason for admission and patient medical history will be collected from the patient records.

Any change in insulin dosing per APN and/or physician will be collected.

Medications: All diabetes medication, steroids and acetaminophen use will be recorded.

Behavioral measures: Patient satisfaction surveys will be collected just prior to discharge and/or one week post discharge to assess the experience with the hospital based CGM device and glucose management. Post discharge 2 patient focus groups will be convened with a minimum of 5 patients in each group to assess patients experience and recommendations after participating in the pilot. Two additional focus groups will be convened with providers that include staff nurses, hospitalists and advanced practice nurses from the glucose management team to gather level of satisfaction and recommendations based on their experience.

Data analysis: (See Appendix C for Statistical Analysis Plan)

Potential Risks

The procedure of insertion and retraction of the needle and the sensor placement itself may cause redness, edema, and/or bruising at the site of insertion. Local infection at insertion site, erythema, inflammation, bleeding, or hematoma are also possible. The frequency of these last events is very low.

Once the sensor is removed, irritation at the site may be present. This may be due to the adhesive (MARSI or Medical Adhesive Related Skin Injuries). This reaction should resolve within a few days to a week. Patients may experience itching at the area which is normal as part of the healing process. These possible expected risks will be assessed with the 1 week f/u call.

There is a remote chance that the sensor or introducer needle could break if insertion is performed improperly. A minor procedure similar to removing a splinter may be required to retrieve the fragment. To minimize the risk associated with this procedure, only trained personnel will perform the insertion of the sensor.

Rarely participants may develop an allergic reaction to any component of the sensor and/or transmitter. This is similar to allergies that occur due to medical tape. If this occurs, then the device will be withdrawn and the patient will be discontinued from participation.

Fingersticks are part of regular patient care. An increased number of fingersticks may take place if the CGM values are not within goal or if there are downward or upward rate of change arrows. Fingersticks may cause pain and/or a bruise.

Hypoglycemia and/or hyperglycemia may occur during the course of the study. Hypoglycemia may be associated with reduced cognitive, diaphoresis, tachycardia, coma and seizure. Symptoms of hyperglycemia may be associated with thirst, glycosuria, ketoacidosis, and hyperosmolar coma. The risk of these complications is an inherent risk of having diabetes. Close follow-up during patient participation will minimize these risks.

Patient blood glucose information will be viewed by specific Scripps staff. The creation of Dexcom share accounts will be established by Scripps research staff. No patient information will be entered within the apps. All info will be coded.

All research staff will complete human subjects' research training prior to their involvement. There are no other known risks.

All data collected are for research purposes only and findings will be presented only in aggregate form. No identifiable information on individuals will be used in reports or manuscripts. To ensure confidentiality, data will be kept in locked files when not in use and will be properly stored at the Scripps Whittier Diabetes Institute. Participants will be assigned identification numbers for data management and data will be identified only by these numbers. A master list of identification numbers, names, and contact information will be kept separate from data in a locked file cabinet at the Scripps Whittier Diabetes and/or in a secure file. This list will never be stored with the participants' data, and will be accessible only to the investigators and trained project assistants.

Study records will be stored in the clinical trials office at Scripps Whittier Diabetes Institute.

Potential Benefits

The anticipated potential benefit in joining the study includes improved glucose management during hospitalization with decreased incidence of hypo and hyperglycemic events. The patient may also learn more about self-diabetes management while participating in the study. However, there is no guarantee that participants will incur any personal benefit from participating in the study. The information learned from this study may help improve the way diabetes is managed within a hospital setting.

Adverse Events (AE):

Overview of rating severity and relationship of AE to Study Device: An adverse event is an event that was not present when the patient was consented. The event can be an acute event, like cough or cold symptoms or worsening of symptoms (in this case an example would be recurrent MI after the patient was admitted for an MI). For study purposes, adverse events will be collected in relation to CGM device use. Serious adverse event can include a significant medical event (ie. severe hypoglycemia, etc).

PI or sub-I will determine the relationship of the AE to CGM use and/or APN-S as not related, possibly related or probably related. Information regarding action taken (none, CGM interrupted, CGM discontinued, or none, APN-S interrupted, APN-S discontinued) will also be collected. Severity (mild, moderate, severe) and outcome (resolved, resolved with sequelae, ongoing, death)

will also be assessed. Information regarding the use of a medication for the AE will also be collected.

Adverse Device Effect (ADE): May include redness, bruising, etc. May also include malfunction of the sensor, transmitter, phone or Dexcom share. AE charting will be done as above.

Serious Adverse Device Effect (SADE): If the PI or sub-I find the ADE to be serious, then the event will go under SADE. AE charting will be done as above.

Serious Unexpected Adverse Device Event (SUADE): If the PI or sub-I find the ADE to be serious and unexpected, then the event will go under SUADE. AE charting will be done as above.

Serious Adverse Event (SAE): Any event of severe hypoglycemia (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) will be collected. Any significant medical event will also be collected.

Confidentiality Procedures

Data to be published or made public will not contain any identifying information. Demographic information will be seen only by the research staff and individuals managing the patient health during hospitalization. The participants will be assigned an identifying number, instead of their names, to ensure their privacy. All data will be transported in locked boxes to the clinical research office at Scripps Whittier Diabetes Institute, where these items and the rest of the study files will be stored in a locked office. The study researchers and their research team, sponsoring agency, government research agencies, and the Scripps IRB are the only ones allowed access to any information from this study. The documents obtained in relation to and during the study will be held for 7 years after study completion. Data that may be entered in databases will be kept in Scripps encrypted computer systems. All data will be de-identified for analyses. If data is to be transferred to any of the facilities specified above, it will be de-identifiable data.

Costs to Subjects

Participants will not incur any cost for participation.

Compensation

Participants will not receive any compensation as part of study participation.

Timeline

Study implementation steps	**- 3 months**	**0 months**	**0 – 5 months**	**0 - 60 months**	**60**	**60 – 70 months**
Obtain CGM Share Direct devices, sensors and transmitters	x					
Train hospital glucose management teams and telemetry monitoring teams in device placement and protocol	x					
Introduce devices and protocol to hospital RN and MD staff	x					
Begin patient enrollment, consenting and data safety and monitoring (each hospital enrollment may start at different times)		x				

Pilot enrollment and data gathering			x			
Ongoing data safety and monitoring review				x		
Patient enrollment ends					x	
Data compilation from the electronic data warehouse				x		
Data analysis				x		x
Patient and provider focus groups				x		x
Final report & Dissemination of results						x

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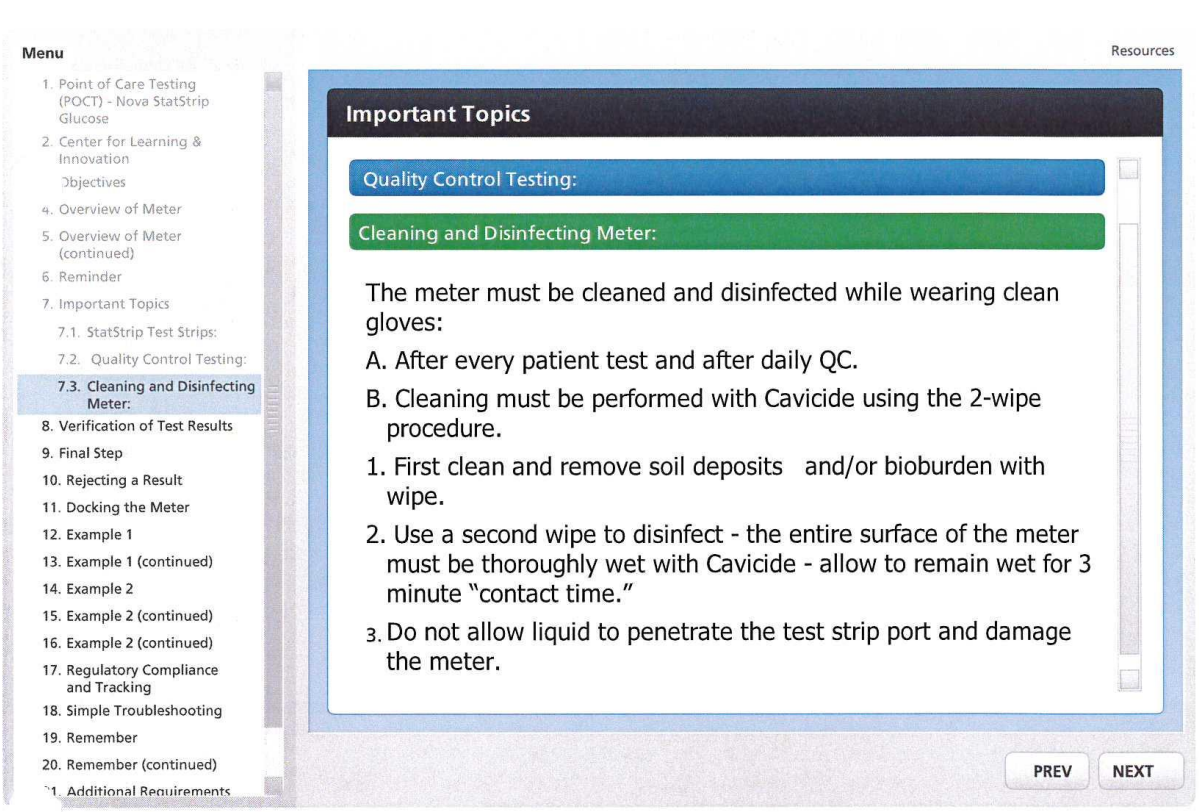
Emory University School Of Medicine, Atlanta, GA, USA. Tuesday, Sep 24, 2013, 3:30 PM - 3:45 PM

13. EASD OP59-The safety and efficacy of a subcutaneous continuous glucose monitoring system compared to point of care measurement in critically ill patients: a randomised controlled trial. D.T. Boom, S. Rijkenberg, S. Kreder, M.K. Sechterberger, P.H.J. van der Voort; Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands, Internal Medicine, Academic Medical Centre Amsterdam, Amsterdam, Netherlands. Tuesday, Sep 24, 2013, 4:00 PM - 4:15 PM

14. EASD OP60- Continuous glucose monitoring at the intensive care unit: nursing workload reduction and cost-benefit analysis. M.K. Sechterberger, J.H. DeVries, P.H.J. van der Voort; Internal Medicine, Academic Medical Centre, Amsterdam, Netherlands, Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands. Tuesday, Sep 24, 2013, 4:15 PM - 4:30 PM

15. Dexcom Investigator's brochure for Dexcom Investigational Use Only Continuous Glucose Monitoring (IUO CGM) System, 2018

Appendix A



From Scripps LMS

2014 Point of Care Testing (POCT) Nova ~~StatStrip~~ Glucose

Appendix B

Scripps **RESEARCH PATIENTS ONLY**

INSULIN, SUBCUTANEOUS ORDERS-
SUPPLEMENTAL ORDERS
ADULT, NON-PREGNANT PATIENTS

PATIENT NAME _____
DATE OF BIRTH (DOB) _____
MEDICAL RECORD NUMBER(MRN) _____
ACCT NO(CSN) _____

Orders preceded with a box must be checked to activate. All other orders are effective unless modified. Complete blanks to specify information not predefined. Initial each modification made to the order set, e.g., additions, deletions, strikeouts. Initial each internal page in bottom right corner. Statements in italics represent decision support for providers completing the order set; these statements are not part of the physician order(s). Provide corporate identification, sign, date and time last page.

Must be on Continuous Glucose Monitor Research Protocol and must be implemented in coordination with Diabetes APRN.

1. Maintain current subcutaneous insulin order set and insure that it includes an HS correction option.
2. Implement the below orders in addition to currently active insulin order set.
3. Obtain additional finger stick blood glucose as indicated per research protocol and/or directed by diabetes research team or designee.
4. For any finger stick blood glucose between 70-79 mg/dL, give 1 tube (15 gm) glucose gel PO STAT or for patients unable to take PO, give D50W 25mL IVP STAT; recheck blood glucose 15 minutes after administration of glucose gel or D50W.
5. If at any point after HS and before 4 am fingerstick blood glucose is greater than or equal to 200 mg/dL and no correction dose given in last three hours, administer correction dose per selected scale below.

Correction Coverage: Insulin Lispro (Humalog) subcutaneously per selected scale **and** blood glucose value:

Blood Glucose (Default Scale)	**Insulin Scale**			
	☐ **Very Low**	☐ **Low**	☐ **Moderate**	☐ **High**
201-250 mg/dL	1 unit	2 units	3 units	4 units
251-300 mg/dL	2 units	3 units	5 units	6 units
301-350 mg/dL	2 units	4 units	6 units	8 units
351-400 mg/dL	3 units	5 units	8 units	10 units
Greater than 400 mg/dL	3 units	6 units	9 units	12 units

6. Above orders to be discontinued when patient is discontinued from CGM research study.

Prescriber Signature	Printed Name or Corporate ID	Date and Time			
Transcriber Signature	Printed Name or Corporate ID	Date and Time	RN Signature	Printed Name or Corporate ID	Date and Time

1PO

PO 100-NS8720-399SW

Appendix C

Statistical Analysis Plan

Statistical analysis was conducted in a subset of N=110 participants with T2D using Dexcom G6 and N=47 participants with T1D using Dexcom G6.

Baseline demographics will be determined to describe the population of patients served over the five year time period. For both type 1 and type 2 patients, glucose data will be analyzed for percentage of CGM values in the target range (70-250 mg/dl), rates of hypoglycemia (<70 mg/dL) and rates of hyperglycemia (>250 and 300 mg/dL). IBM SPSS Statistics v24 will be used to calculate individual and group rates for the specified outcomes; group means will be compared using ANCOVA procedures that incorporate relevant covariates (e.g., age, gender, length of stay).

Sample Size

IBM SPSS Sample Power 3 was used to calculate the projected sample size needed in patients with type 2 diabetes to detect a 4.2% absolute difference (5% relative difference) between groups for the diabetes type 2 primary outcome [Aim 2] (i.e., % of CGM readings in the target range of 70-250 mg/dL). The comparison/baseline effect size was estimated at 85.4% based on pilot data in the target population, resulting in a target outcome of 89.6% based on the above-stated difference between groups. With a sample size of N=110 and alpha of .05, power will be 0.80 to detect this effect size, thus indicating adequate statistical power for our diabetes type 2 primary aim (Aim 2). This sample size will also provide sufficient power to examine secondary outcomes, percentage of values < 70 and >300 mg/dL; the between-group comparison of percentage of values < 250 mg/dL will remain purely exploratory.

Analyses

Of the early participants enrolled, Dexcom G4 and G5 CGM devices were used. Pilot analyses of TIR were conducted and reported as preliminary outcomes. A full evaluation and analyses were conducted on a subset of the total enrolled participants who were placed on Dexcom G6 devices.

Analyses of T2D Subgroup:

A total of 110 adults ≥18 years old, Spanish or English speaking, with type 2 diabetes (T2D) and three POC or serum values >200 mg/dL in the last 24 h, requiring subcutaneous insulin, were admitted to a non–intensive care unit (ICU) floor at Scripps Mercy Hospital (San Diego, CA) and enrolled in an RCT for ≥18 h. Pregnancy, intravenous insulin, adhesive allergy, anticipated computed tomography/MRI/diathermy procedures in next 24 h, or any condition deemed contraindicated were reasons for exclusion. The Scripps Health Institutional Review Board (San Diego, CA) approved the study.

After informed consent, enrollment, and randomization, a Dexcom G6 was placed by a research assistant or nurse. Blinded CGM data were used for evaluation only in usual care (UC) (standard POC testing protocol;*n*= 53). Data in the RT-CGM group (*n*= 57) were wirelessly transmitted from a bedside smartphone to secure Health Insurance Portability and Accountability Act–compliant, monitoring platforms: Dexcom FOLLOW and CLARITY. To target a hospital time in range (TIR) of 70–250 mg/dL, hospital telemetry monitored RT-CGM data in FOLLOW on an iPad and notified nursing of hyperglycemia (>250 mg/dL, 9:00 p.m.–4:00 a.m.) and trends toward hypoglycemia (<90 mg/dL, 24 h/day) for rapid treatment per protocol (Real-Time Adjustments. Of note, because CGM was not U.S. Food and Drug Administration–approved for hospital use, confirmatory POC testing was conducted before treatment, and RT-CGM participants were still monitored via the hospital's standard POC protocol (~4 times/day). All previous antihyperglycemic agents were discontinued, and participants were placed on the hospital subcutaneous insulin protocol to standardize glucose management across groups. A diabetes advanced practice nurse conducted the POC review for all participants and remotely monitored CGM trends in CLARITY and collaborated with hospitalists to make standardized algorithm-based insulin adjustments using trends noted to optimize therapy in the RT-CGM only (Daily Adjustments).

Baseline characteristics were examined to evaluate randomization using χ^2,*t*, and Mann-Whitney tests. Restricted maximum likelihood was used in a linear effects model to evaluate concordance between CGM and POC values. Participant-level CGM metrics included CGM duration, glucose mean, SD, and coefficient of variation, and percentage of TIR (70–180, 70–200, 70–250 mg/dL) and time in hyperglycemia (>250, 300 mg/dL) and hypoglycemia (<70, 54 mg/dL). Outcomes were tested in unadjusted linear regression models with group as a fixed effect, unless otherwise specified. Results reported in the text are regression coefficients (β) for the group effect and represent expected mean differences between RT-CGM (coded 1) and UC (coded 0). Hypoglycemic events (≥20 min <54 or 70 mg/dL) were descriptively analyzed to document the number of participants with one or more event and the number/participant and event duration. All analyses were conducted in R 3.5.3 software.

Analyses of T1D Observational Subgroup:

Continuous glucose monitoring as SOC data are entered in Research Electronic Data Capture (REDCap). Patient data are obtained via the EMR through an automated data acquisition platform built into Snowflake Data Cloud (Snowflake Inc, Bozeman MT). Continuous glucose monitoring data for each encounter are downloaded via Dexcom CLARITY.

Data are presented for type 1 diabetes (T1D). Data are presented descriptively. Categorical data are described as frequencies/percentages, and continuous data as means and standard deviations, or medians and interquartile ranges (IQRs), if skewed. Encounter-level CGM metrics included CGM duration, glucose mean and standard deviation, coefficient of variation, and several TIR,

time-above-range, and time-below-range metrics, as well as hypoglycemic events (as previously described). The POCT/CGM concordance was calculated using encounter-level and overall mean absolute relative differences (MARDs) and is displayed via a Clarke Error Grid (CEG) using the “ega” package in R. Comorbidity data were reported based on International Classification of Diseases (ICD) code classification using the “comorbidity” package in R.

All data processing and analyses were conducted in R v. 4.0.3.