Study Title	Expanding use of continuous glucose monitoring beyond COVID in critical care: Impact on nurse work patterns and patient outcomes
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Research Protocol

Expanding use of continuous glucose monitoring beyond COVID in critical care: Impact on nurse work patterns and patient outcomes

I. Objectives

The **primary objective** of this mixed methods hybrid II implementation study is to assess the feasibility of real time continuous glucose monitoring (CGM) implementation using a CGM plus (+) point-of-care (POC) protocol among patients on IV insulin or those with hyperglycemia (>250mg/dl) in the critical care hospital environments. Use of the hybrid II implementation study design will allow simultaneous evaluation of implementation and effectiveness outcomes to promote more rapid adoption of CGM as routine care for hospitalized patients.

The research Questions (RQ) we hope to address in this study are:

RQ 1: Establish the clinical utility, fidelity, and adoption of Dexcom G6 CGM as a tool for making dosing decisions within a CGM+POC protocol among medical intensive care unit (MICU) patients. We will conduct a prospective observational cohort study among MICU patients using Dexcom G6 CGM therapy (N=100). *Clinical utility criteria*: Time to CGM validation within protocol parameters, mean percent of dosing decisions determined by CGM, changes in insulin dosing from standard guideline or outside standard times in response to alarm and/or trend data (as measured by manufacturer download data and corresponding electronic health record (EHR) documentation). *Fidelity criteria*: Proportion of times CGM used non-adjunctively/number of times non-adjunctive use indicated per protocol. *Adoption criteria*: Proportion of patients who consent to received initial CGM monitoring/number of patients eligible to receive initial CGM monitoring. **Hypothesis:** The majority of insulin dosing decisions will be made using non-adjunctive CGM and CGM will alter nursing dosing decisions from standard guidelines.

RQ 2: Assess the effects of CGM implementation on nursing workload and factors influencing nursing care delivery. We examine nursing workload and care delivery factors through surveys administered to MICU nurses and through a MICU staff nurse focus group (N=10). *Nursing care delivery factors:* Acceptability of CGM measured by the Acceptability of Intervention Measure (AIM), appropriateness of CGM measured by the intervention appropriateness measure (IAM), and feasibility, measured by the Feasibility of Intervention Measure (FIM). Nursing care delivery factors, evaluation of CGM support, and CGM knowledge will be evaluated through focus groups and CGM Satisfaction Questionnaire (modified for healthcare workers). **Hypothesis:** The use of CGM will significantly reduce nursing workload while increasing frequency of glucose monitoring.

RQ 3: To assess glycemic control among patients receiving CGM in the CGM enabled MICU compared to historical control patients who received POC glucose monitoring in the MICU. Among critically ill patients on CGM (N=100) we will examine time in range (70-180mg/dl), time 100-180mg/dl, time 140-180mg/dl, time in hypoglycemia (<55mg/dl, <70mg/dl), and time in hyperglycemia (180-250mg/dl, >250mg/dl) compared to matched historical control patients using 3-tiered linear mixed models to control for patient, unit, and nurse specific variability. **Hypothesis:** Patients with CGM will exhibit greater time in range (100-180mg/dl, 140-180mg/dl, 70-180mg/dl) and experience less frequent time in hypoglycemia than patients on fingerstick POC.

RQ 4: (exploratory) To assess hospitalization outcomes and conduct economic evaluation of the costs to deliver CGM implementation in the MICU. We will track time and resources needed for CGM implementation including personnel, training, facilities, materials, equipment, and other necessary inputs. *Hospitalization outcomes criteria*: Length of stay [ICU, total stay], cost of stay, cost of CGM vs. standard POC glucose monitoring, discharge level of care [home, SNF], 30-day readmission, morbidity, and mortality. **Hypothesis:** Patients with CGM will experience shorter length of stay, lower cost of stay, will be more likely to discharge to home vs. SNF,

have lower 30-day readmission rate, and experience lower mortality/morbidity than matched historical control patients receiving fingerstick POC in the MICU.

II. Background and Rationale

During the COVID-19 pandemic, CGM has provided a means for reducing healthcare worker exposure to the virus and a reduction in care delivery burden during a period of staffing crisis. In April 2020, the FDA issued a statement indicating they would permit the use of these systems within the hospital setting during the pandemic.[1] Since then, CGM has been integrated into routine care within The Ohio State University Wexner Medical Center (OSUWMC) MICU.[2] OSUWMC began using CGM within a hybrid POC plus CGM protocol in May of 2020 and have demonstrated successful and safe use of these devices within the health system for over 132 MICU patients.[3] In concert, other health systems across the United States have used inpatient CGM and have disseminated valuable real-world data that demonstrates safe and effective inpatient use of the technology within a hybrid point-of-care (POC) plus CGM protocol.[4-10] Across all of these studies, no adverse events were reported. While these studies did demonstrate a reduction in POC glucose testing, reasonable accuracy, and safe use among critically ill COVID-19 patient, they were limited by small sample sizes and a restricted patient population.

At our institution we examined data from the initial cohort of 19 COVID-19 patients to use CGM in OSUWMC MICU. Among these patients, 89% were on ventilators, 37% on vasopressors, and 42% on hemodialysis at the time of sensor placement.[11] Despite the severity of critical illness, MARD was 13.9% with no apparent association with oxygen saturation, mean arterial pressure, vasopressor use, renal replacement, anticoagulation, or ventilator support. Time in range (70-180 mg/dl) on day 1 was 64+/- 23%, and on days 2-7 was 72+/-16%. Time below range (<70 mg/dl) was 1.5+/-4.1% on day 1 and 0.16+/-0.35% on days 2-7 [11]. We have since expanded our analysis to include a larger cohort of the first 50 COVID-19 patients on CGM. Of these patients, 92% were on ventilators, 46% on vasopressors, 33% on hemodialysis, and 74% were on steroids at the time of sensor placement. In our larger cohort, the aforementioned factors were again not associated with sensor accuracy. Hybrid protocols of POC glucose checks with CGM use have been used in other small studies of extremely critically ill ICU patients with COVID-19 (n=61 subjects total in four studies)[5-7,10]. One study did find decreased accuracy with cardiac arrest.[5] Across these studies, MARD ranged between 11.1-13.9% for Dexcom G6[6,10,11] and Clarke error grid analysis showed 98-98.2% in zones A+B.[6,10] In a recent larger study conducted among 218 hospitalized non-ICU patients, mild to moderate anemia was not shown to impact sensor accuracy, however more severe anemia (hemoglobin <7g/dL) was found to correlate with higher ARD (17.8%).[12] This same study demonstrated no association between hyperglycemia and sensor accuracy but did demonstrated a slight increase in MARD (18.8%) and ARD (14.5%) with glucose <70mg/dl.[12] In a study by Boom et al. focused on hypoglycemia reduction, 177 medical ICU patients were randomized to CGM or standard of care. In this study, hypoglycemia and was reduced from 12 times per day to fewer than 1 time per day and overall glucose control was similar between groups.[13] Other ICU studies have also showed acceptable accuracy in ICU patients, despite the use of older technologies.[14,15] Moreover, there is evidence that accuracy can be offset by increased frequency of monitoring, as is the case with CGM.[16] While there is some concern surrounding the effects of edema or changes in fluid volume on sensor accuracy, a study among congestive heart failure patients demonstrated no association between MARD and BNP or changes in plasma volume, this despite the use of older less accurate technology.[17]

Diabetes is a worsening epidemic worldwide. In the United States, the prevalence has quadrupled between 1980 and 2020 with an estimated 21.9 million adults living with diabetes [18]. Hospitalizations among patients with diabetes account for 30% of the total medical cost of inpatient care with more than 7.8 million hospital discharges in 2017 in the United States [19]. Hypoglycemia, hyperglycemia, and glycemic variability in the hospital are associated with poor health outcomes including infection, acute renal failure, and death [20-24]. Traditional POC capillary glucose monitoring measures glucose at one point in time and often misses hypoglycemia [23,25,26], especially overnight or asymptomatic episodes, whereas continuous glucose monitoring (CGM) can help provide details of glucose continuously as well as velocity and direction of change over time. The ability to visualize

glucose trends or direction and velocity of glucose offers tremendous additional benefit over traditional discrete POC glucose monitoring.

Additionally, CGM can improve efficiencies in the critical care environment and reduce nursing care burden.[2,13] According to the Bureau of Labor Statistics the United States is facing an unprecedented nursing shortage which is expected to worsen over the upcoming decade. Intensive inpatient POC glucose monitoring is an arduous, time-consuming task, often resulting in insufficient frequency of testing and testing that is mistimed with oral intake or insulin administration.[27] The use of inpatient CGM holds tremendous promise to improve patient outcomes, reduce nursing workload, and associated healthcare costs, however, the inpatient implementation of CGM beyond the pandemic presents unique implementation challenges and warrants further inquiry.

Description of Technology.

The Dexcom G6 CGM (Dexcom Inc) measures interstitial fluid glucose. The G6 system consists of 3 key parts: the sensor wire, a transmitter, and a display device. In addition, a CGM Dashboard will be used to display data at the nurse's stations.

The sensor comprises a water-resistant sensor pod that is worn on the skin, and the sensor wire that is inserted just under the skin (depth is less than 0.5 inches) using the single-use applicator. The sensor can be worn for 10 days and continuously measures glucose levels. In this study the sensor will be worn on the back of the arm.

The transmitter attaches to the sensor pod and sends glucose information to the display device using Bluetooth. Interstitial glucose concentration estimates are sent from the transmitter to the receiving device at 5-minute intervals and can be checked at any time.

The G6 software app is downloaded onto the compatible smart device (Android phone), that is paired with the transmitter before use. The app continuously and automatically sends data to the Dexcom remote server, where the data are stored and displayed in the CLARITY diabetes management software. Alarms for hypoglycemia, hyperglycemia and predicted hypoglycemia will be set per the CGM + POC protocol. Android phones are kept just outside of the patient rooms. The patient's hospital identification label will be placed on the back of the phone to ensure data is correctly matched to patient participant.

In addition to the G6 app, glucoses will be displayed on a laptop computer at the nurse's station using investigational Dashboard software. Investigational, unapproved Dashboard software will allow continuous remote monitoring of Dexcom G6 data from multiple patients on a secondary display at the nurse's station. Individual CGM tracings for each patient wearing Dexcom G6 will be displayed simultaneously on the investigational Dashboard software for multiplex remote monitoring. The Dashboard is programmed with trend arrows, an alarm, and glucose threshold alerts to facilitate real-time surveillance of impending hypo and hyperglycemia that warrants prevention or intervention. Treatment decisions will not be made using data displayed on this software; glucose will be confirmed on G6 app before treatment decisions are made.

CGM + POC Protocol.

A CGM + POC protocol was developed and implemented within OSUWMC MICU unit. The protocol, which allows for intermittent non-adjunctive CGM use with requisite initial validation within each patient and continued validation Q6 hours, proved successful in facilitating safe and effective CGM implementation in over 132 critically ill patients with COVID-19. The CGM + POC protocol require comparison of paired sensor-meter readings. The comparison standard method (Novo StatStrip POC meter) and source (capillary, arterial, venous) are FDA approved for inpatient use. In an effort to mitigate risk in this study among critically ill MICU patients, we propose a more conservative strategy with increased frequency of ongoing POC testing and validation every 4 hours. Additionally, more frequent testing at Q2 or Q1 hours will occur during periods of clinical change that could proceed a decline in CGM accuracy. The standard is compared to the CGM value obtained within 5 minutes. The threshold criterion for nonadjunctive (stand-alone) use of the CGM to inform insulin dosing decisions appears in Table 1. CGM values will be used to determine insulin doses within standard OSUWMC guidelines (e.g., IV infusion guideline) and provider prescribed orders. Alert thresholds are set at 100 mg/dl (lower threshold) and 300

mg/dl (upper threshold). In addition, the Urgent Low Soon alert will be activated and designed to provide a 20-minute advance warning of impending hypoglycemia, so nurses can act quickly to avoid a potential severe hypoglycemic event.

Table 1. Initial and Ongoing CGM Validation

Stage	POC glucose testing procedures
CGM validation	POC glucose testing Q1 hour compared to CGM glucose Proceed to Q4 hour POC testing when <u>two</u> consecutive sensor-meter pairs approximately 1-hour apart meet either of the following criteria: 1) CGM <20% difference from the POC when the glucose is >100 mg/dl 2) CGM <20 mg/dl difference from the POC when the glucose is <100 mg/dl
Sustained use	Revert from Q4 hour to Q1 hour POC testing if: 1) CGM >20% difference from the POC when the glucose is >100 mg/dl 2) CGM >20 mg/dl difference from the POC when the glucose is <100 mg/dl 3) Revert back to Q4 hour POC testing when <u>two</u> consecutive sensor-meter pairs approximately 1-hour apart meet the initial validation criteria Revert from Q4 hour to Q2 hour POC testing for a duration of 6 hours for one of the following clinical status events occurring in isolation: 4) Intubation 5) Pressor support initiated (Levophed dose <0.5 mcg/kg/min or equivalent) 6) New cardiovascular event (MI, CVA) 7) Initiation or discontinuation of nutrition support (i.e., enteral feed, total parenteral nutrition) 8) Hemoglobin <7g/dL 9) CGM or POC glucose <70mg/dl (follow OSUWMC hypoglycemia policy for initial treatment and monitoring) 10) Predicted low alert (glucose predicted to be <55mg/dl in the following 20 minutes) 11) Acidosis with pH <7.3 12) Signs and symptoms do not match glucose readings, particularly for hypoglycemia Revert from Q4 hour to Q1 hour POC testing for a duration of 6 hours for two or more of the above clinical status events occurring together (example: patient is intubated and starts pressor support) If after 6 hours no additional clinical scenarios featured above have developed than Q4 hour POC testing can resume after initial validation using two consecutive sensor-meter pairs. Obtain 1 time POC glucose if: 13) No glucose value appears on android screen (due to signal loss, Low/High measure) 14) Low threshold alert (<100mg/dl)
Stop CGM use	Stop use of CGM for insulin titration or glucose monitoring and revert from Q4 hour to Q1 hour POC testing (**do not remove CGM sensor until sensor expires**) for the following conditions: 1) Refractory shock (Levophed dose >0.5 mcg/kg/min or equivalent) 2) Cardiac arrest 3) Newly developed diabetic ketoacidosis (DKA) (pH <7.3 or serum bicarbonate <15 mEq/L in the setting of elevated ketones) 4) Newly developed hyperosmolar non-ketoacidosis (HONK) 5) Pitting edema, anasarca, blue or purple discoloration to bilateral upper extremity 6) Initiation of treatment with high dose acetaminophen (>1 gram Q6 hours) Initiation of treatment with hydroxyurea

III. Procedures

A. Research Design

<u>Hybrid Research Design</u>

A hybrid research design that combines elements of effectiveness and implementation research will be used to enable more rapid adoption of CGM as standard of care. Traditional step-wise approaches to research which progress from clinical efficacy research, to clinical effectiveness research, and finally implementation research limit application and slow routine uptake in real-world environments. A hybrid research II design allows for two objectives within the research with equal emphasis placed on (1) testing the effectiveness of the intervention and (2) determining feasibility and potential impact of the implementation strategy. The use of this design allows us to craft a blueprint for successful deployment of CGM therapy within health systems, while at the same time gathering valuable real-world effectiveness data. It also allows us to examine how clinical outcomes relate to levels of adoption and fidelity.

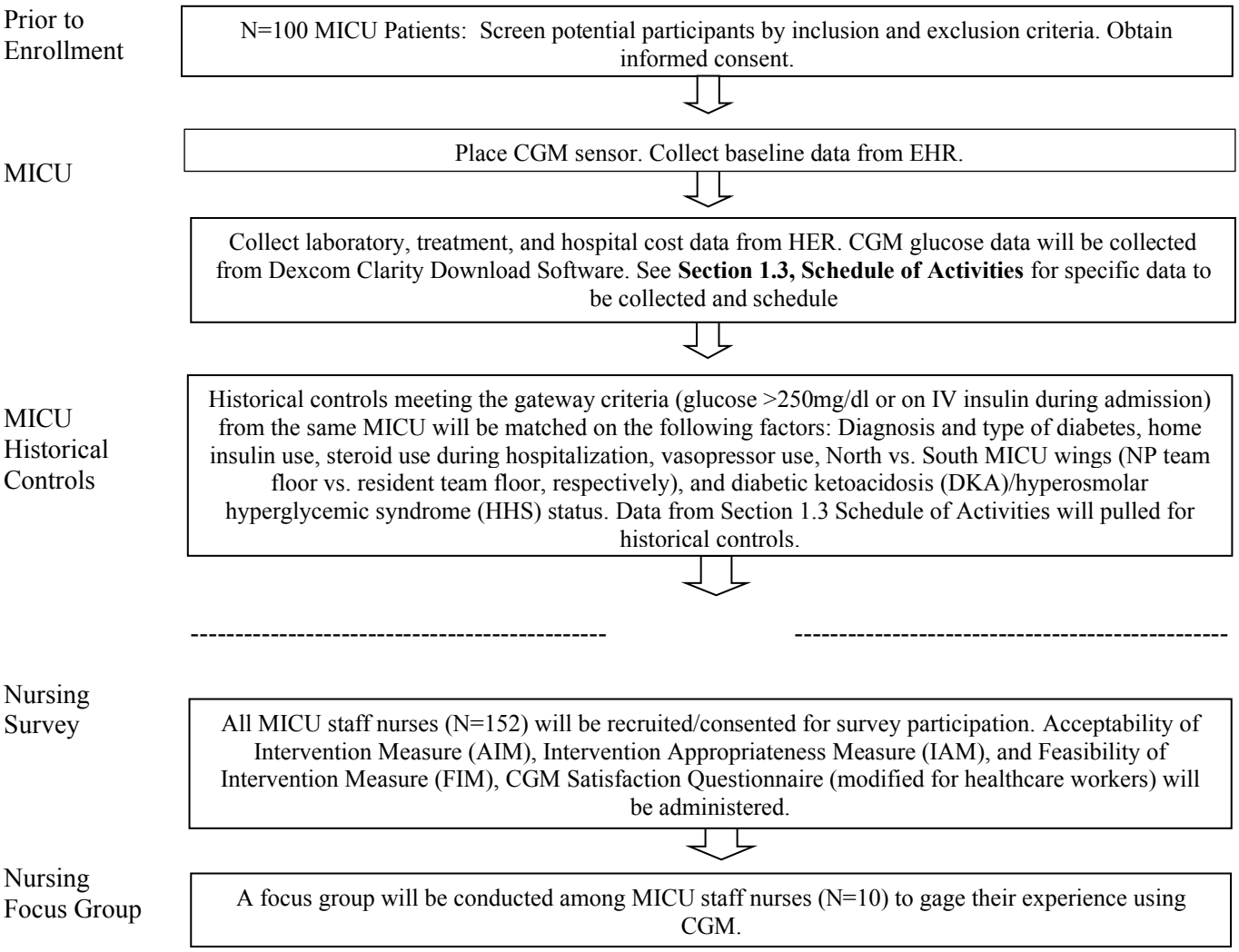
APPROACH. Overview: This proposal analyzes the feasibility of inpatient real time CGM implementation through the use of a CGM + POC protocol as routine care for glycemic monitoring among patients with hyperglycemia (>250mg/dl). The research addresses essential components of ICU implementation including the clinical utility of the system to inform glycemic management and insulin dose administration (Aim 1), effects on nursing workflow and care delivery (Aim 2), and effects on patient glycemic control compared to matched historical control patients from the MICU who received fingerstick POC. Additionally, we propose an exploratory aim to examine the effects of CGM use on hospital associated outcomes including length of stay, cost of stay, cost of CGM vs. POC glucose monitoring, discharge level of care, 30-day readmission rates, morbidity and mortality compared to matched historical control patients (Aim 4). The study will be conducted using a staggered enrollment of 20 patients in each wave (20% of target enrollment) with a respite between waves to allow analysis of safety and fidelity data prior to continued enrollment. The initial wave (n=20) will be conducted as a "pilot" with full analysis including examination of benchmark criteria study continuation. If pilot analysis demonstrates safe use and fidelity, then subsequent recruitment will proceed. The analytic approach for each Aim is described below. STATA 15.0 (StataCorp, College Station, TX) will be used for quantitative analysis and NVIVO (version 10, Doncaster, Australia) will be used for qualitative data management.

Table 2. Study Timeline

Activity	Pre-award			Year 1						Year 2					
FDA & IRB submission & approvals															
Nursing union approvals															
Patient recruitment															
CGM data collection															
EHR data collection															
Nursing recruitment															
Nursing focus group & surveys															
Analysis															
Manuscript & conference dissemination															
Aim 1 & 3: ICU Clinical Utility/Implementation & Glycemic control															
Aim 2: Nursing workload and Care delivery															
Aim 4: Hospital outcomes															

FDA

Figure 1. Study Flow Diagram



B. Sample

The study will take place at OSUWMC. At OSUWMC there are approximately 13,000 hospitalizations with a diagnosis code for diabetes each year and current annual inpatient diabetes consult service and diabetes educator consults are roughly 3000 per year. OSUWMC has implemented a comprehensive, hospital-wide inpatient diabetes program since 2006, including streamlined computerized diabetes related order sets, carbohydrate-based insulin dosing, education, and ongoing review of outcomes. OSUWMC converted to EPIC EHR in 2011 for both inpatient and outpatient electronic medical records. The medical centers MICU has been utilizing Dexcom G6 CGM for COVID-19 patients since May of 2020 and to date has utilized CGM in over 132 critically ill COVID-19 patients. The study will take place in the MICU. The MICU is a 48-bed critical care center and employs 152 staff nurses. Patients will be identified through daily screening of patients and associated glycemic control in the MICU to identify potential participants with hyperglycemia (glucose >250mg/dl) or those currently on IV insulin. In 2019, prior to the COVID-19 pandemic, OSUWMC had 1,065 unique patient admissions in which the patient had a glucose >250mg/dl over the course of their MICU stay. Within the MICU patient population, patients with more severe illness and those with conditions that may interfere with CGM sensor accuracy will be excluded from participation. Full inclusion and exclusion criteria are as follows:

Eligible individuals are:

1) adults >18 years old,
2) admitted to OSUWMC MICU and

3) have hyperglycemia (glucose >250mg/dl) or are currently on IV insulin.

Non-eligible individuals are:

7) Current COVID-19 infection,
8) Refractory shock (Levophed dose >0.5 mcg/kg/min or equivalent)
9) Actively being treated for diabetic ketoacidosis (DKA)
10) Actively being treated for hyperosmolar non-ketoacidosis (HONK)
11) Pitting edema, anasarca, blue or purple discoloration to left upper extremity
12) Treated with high dose acetaminophen (>1 gram Q6 hours)
13) Treated with hydroxyurea
14) Are pregnant, patients
15) Using home insulin pump therapy during hospitalization, or
16) Reside in a corrections institution.

Sample Size Justification. The primary outcome for the power analysis is the percentage of time spent in target (70-180mg/dl). We estimate from previous studies[13,28] that these values may have a standard deviation as high as 25 percentage points, in which case with 100 patients in each group we will have 80% power to detect a difference of 10 percentage points in time in range (e.g., 65 vs. 75); a moderate effect size of 0.4. If the standard deviation is lower (e.g., 15 as has been true in some studies), we will have greater power (99%) to detect a 10 point difference and are still well powered to detect smaller differences (e.g., 90% power for a 7 point difference). All power calculations assume an alpha of 0.05 and minimal statistical effects of clustering within the hospitals (e.g., unit or nurse level).

C. Detailed study procedures

Recruitment: Critical care clinical research coordinators will screen for preliminary eligibility and forward potential participant names to study team using a secure medical record in-basket process. The study team will determine eligibility. The study team will ask for permission for the patient to be approached. If permission is granted, the study team will verify eligibility and obtain informed consent from the patient or the patient's legally authorized representative. Consent will be obtained prior to research participation and CGM placement. Recruitment is expected at a rate of 5 patients per week over seven months. Our target recruitment will be 100 MICU patients.

Nurse training: OSUWMC MICU nurses have significant experience with CGM use in an extremely ill cohort of COVID-19 patients. Each nurse in the MICU receives training on CGM set-up, insertion, pairing, and CGM glucose monitoring features as part of their annual critical care competencies. OSUWMC MICU nurses are trained and experienced in using POC glucose measurement to validate the CGM system, however the protocol at use in this study differs somewhat from the COVID-19 protocol currently at use in the MICU. Given that, nurses will receive training on distinctions between the two protocols including changes to the frequency of POC testing, the addition of clinical status events that would warrant more frequent POC testing and validation (Q1 or Q2 hours depending on number of events present for a duration of 6 hours). New criteria to stop clinical use (i.e., no use of CGM for glucose monitoring, no use of CGM for insulin titration) will be reviewed in detail with nursing along with plans for the sensor to remain in place only for data collection. Nursing trainings will be conducted by PI (Faulds), Co-I (Jones), and study coordinator during staff meetings and nursing huddles conducted on all shifts. All nurses will receive training on the new protocol prior to patient recruitment. The study protocol, along with currently available training materials, will be kept at the bedside of all patient participants.

Staggered enrollment and initial pilot: We will stagger enrollment with just 20 patient participants over a 4-week period (target 5 participants/week with a respite between enrollment to allow analysis of safety and fidelity data prior to the next round. A robust analysis would be conducted after this first "pilot" round of enrollment. Accuracy analysis would include MARD and Clark Error Grid. A full assessment of protocol adherence and evaluate adherence to standard insulin dosing guidelines will be completed. The pilot analysis will include evaluation of

benchmarks for accuracy, safety, and adverse event monitoring with benchmarks that must met prior to subsequent enrollment. Pilot benchmarks for study continuation are as follows:

- Successful initial validation criteria within 24 hours in 80% of participants (16/20)
- Clark error grid analysis demonstrating >95% points in zone A (within 20% of reference glucose value) or zone B (outside of 20% but would not lead to inappropriate treatment) following initial validation.
- No more than 1 episode of inappropriate insulin dose resulting in severe hypoglycemia (glucose <55mg/dl) after initial sensor validation
- No more than 1 episodes of iatrogenic DKA (pH <7.3 or serum bicarbonate <15 mEq/L in the setting of elevated ketones) or hyperosmolar nonketotic state (osmolality ≥320mOsm/kg with BG >600mg/dl and pH >7.3 or serum bicarbonate >15 mEq/L)
- No episodes of severe adverse events resulting in prolonged hospitalization, or other life-threatening complication that attributed to the study intervention
- No severe adverse events resulting in death, or other life-threatening complication that is attributed to the study intervention
- No severe adverse event resulting in prolonged hospitalization, or other life-threatening complication that attributed to the study intervention and is expected to recur

Oversight and monitoring. Study team oversight of nursing use of the CGM system will be performed through a combination of (1) daily evaluation of EHR and CGM Clarity data and (2) through rounding on CGM patients (mon-Friday by PI (Faulds), Co-I (Jones) and/or study coordinator (to be named) (Saturday, Sunday and holidays by the MICU charge nurse who will communicate that day with study team members. Daily rounds will allow the study team to continuously evaluate protocol fidelity and identify any safety concerns. The study staff will evaluate CGM use daily through Clarity CGM and EHR data to determine the following:

3. Was initial validation criteria achieved correctly and at what frequency
4. Is ongoing validations performed Q4 hours and according to validation criteria
5. If validation is met did the nurse begin hybrid use with non-adjunctive CGM use
6. Using clarity reports study staff will assess the presence of alarms (e.g., <100mg/dl, >300mg/dl, predictive hypoglycemia) Alarms will be reviewed daily by research staff to ensure hypoglycemia and hyperglycemia are being treated in accordance with OSUWMC guidelines.
7. Those patterns of hyperglycemia or hypoglycemia assessed every 24 hours, will be reported to primary team via pager/direct message to allow changes to insulin dosing as needed (e.g., max drip rate for IV insulin titration).
8. Assessment of change in clinical status criteria (Table 1) in which per protocol the nurse would increase frequency of POC testing and validation.
9. Assessment of Stop CGM use criteria (Table 1) in which per protocol the nurse would no longer use the CGM for glucose monitoring or insulin titration.

RQ 1: Establish the clinical utility, fidelity, and adoption of Dexcom G6 CGM as a tool for making dosing decisions within a CGM+POC protocol among medical intensive care unit (MICU) patients.

Rationale/Approach. We will conduct a prospective cohort observational analysis among critically ill patients on IV insulin or those with hyperglycemia (>250mg/dl) in OSUWMC MICU. The research will allow us to examine the clinical utility and implementation of CGM as the standard of care in a critical care environment. We hypothesis that the majority of insulin dosing decisions will be made using non-adjunctive CGM and CGM, with the availability of trend and alarm data, will alter nursing dosing decisions from standard guidelines.

Procedures. Once consent is obtained, the MICU staff nurse will insert the Dexcom G6 sensor, set up the system, pair the transmitter on patients, and connect patient data to a centralized nurse's station CGM Dashboard in the MICU (N=100). The CGM + POC protocol will be used to validate at which time the CGM will be used for non-adjunctive insulin dosing decisions. POC testing will be performed Q4 hours for continued validation of the CGM with more frequent sustained POC validation during periods of rapid clinical change (Table 1).

The Android phone, which will receive glucose data from the CGM transmitter, will be kept outside of the patient room allowing the staff nurse to visualize discrete values, trends and hear alarms without entering the patient's room. OSUWMC MICU employs a staffing ratio maximum of 1 nurse for 2 patients. MICU staff nurses will only care for 1 patient using CGM at a time. Alarms are visually displayed and audible from both the dashboard and receiver (Android phone); however nurses are instructed to confirm all glucose values and the presence of alarms on the receiver devices at the bedside prior to treatment. All nurses in the MICU are trained on CGM alarm recognition and response. In a previous analysis, nurses reported alarms were audible throughout the MICU unit.[2] If the nurse assigned to the CGM patient participant is not immediately available when an alarm is sounding, another nurse or the charge nurse is expected to respond to the alarm and provide appropriate treatment. This same alarm response delegation is employed for other MICU systems including cardiac telemetry, Pulse oximetry, and ventilator alerts. Nurses will follow standard approved OSUWMC guidelines, policies and provider dosing orders for treatment of hyperglycemia and hypoglycemic events. Episodes of hypoglycemia and hyperglycemia will be responded to in real time by nursing staff. Our hypoglycemia guideline (Table 3) treats glucose <80mg/dl with Dextrose D50% for critically ill patients. Dosing is stratified based on degree of hypoglycemia with follow-up required within 15 minutes. For hypoglycemia <60mg/dl nurses are instructed to inform the provider via pager/direct chat. Nurses in the MICU are experienced in administration dextrose D50% using the described hypoglycemia protocol. If the patient is ordered to undergo magnetic resonance imaging (MRI), computerized tomography (CT) radiographic procedures, or diathermy than the sensor/transmitter will be removed prior to the procedure as these procedures could potentially interfere with sensor accuracy.[29] A new sensor will be inserted after procedure is completed and will undergo initial validation prior to use.

The patient will remain on CGM for the duration of their hospital stay and if discharged to home may transition to personal use of the Dexcom G6. The Dexcom G6 sensor is replaced every 10 days and will be removed and then replaced for some radiographic procedures or sensor failure. CGM data is automatically transferred to Dexcom's cloud-based Clarity system.

Table 3. OSUWMC Hypoglycemia Guideline, Patients Who are Not Alert, Are NPO, or on IV Insulin Infusion

Blood Glucose (BG) Level*	Action	Follow-Up
60-79 mg/dL	• Administer 7.5 g Dextrose D50% (15 ml) IV* • Consider calling House Officer if patient experiencing recurrent BG <70 mg/dL in past 12 h	• Recheck BG q 15 min following treatment and treat accordingly until ≥ 80mg/dl • Once ≥ 80mg/dl, recheck BG q1h x2 (x4 if <45mg/dL at onset), then resume POC glucose as previously ordered, Patients who are admitted with hypoglycemia should be monitored at least q 4h for a minimum of 24h • If > 4h from initial event and BG ≥ 80mg/dl for two consecutive readings, may consider reducing IV dextrose
45-59 mg/dL	• Administer 12.5 g Dextrose D50% (15 ml) IV* • Call House Officer to report BG and action taken	
<45 mg/dL	• Administer 25 g Dextrose D50% (15 ml) IV* • Call House Officer to report BG and action taken	
ALL	• Consider adding Dextrose 5% to maintenance IV fluids at a rate of ≥50ml/hr or increase rate of existing maintenance IV if dextrose source already present	

Variables and measures. *Clinical utility criteria*: Time to CGM validation within hybrid protocol parameters, mean percent of dosing decisions determined by CGM, changes in insulin dosing from standard guideline or outside standard times in response to alarm and/or trend data (as measured by manufacturer download data and corresponding EHR documentation). *Fidelity criteria*: Proportion of times CGM used non-adjunctively/number of

times non-adjunctive use indicated per protocol. *Adoption criteria*: Proportion of patients approached to received GCM monitoring/number of patients eligible to receive initial CGM monitoring.

RQ 2: To assess the degree to which CGM implementation within the ICU environment effects nursing workload and care delivery.

Rational/Approach. We will conduct a mixed method analysis to evaluate nursing workload and care delivery factors. Nursing care delivery factors including evaluation of CGM support, acceptance of CGM, perceived feasibility, and CGM knowledge, will be evaluated using a combination of questionaries and focus groups.

Procedures/Variables and Measures. We will evaluate *nursing care delivery factors* related to CGM implementation support, acceptance of CGM, feasibility, appropriateness, CGM knowledge and satisfaction with CGM as measured by Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM), CGM Satisfaction Questionnaire (modified for healthcare workers) and focus group conducted among nurses in the CGM-enabled MICU. The AIM, IAM, and FIM are brief 5 item Likert-scale questionaries with each showing a high degree of content validity with alphas for the 3 questionnaires between 0.87 and 0.89.[30] CGM Satisfaction Questionnaire (CGM-SAT) is a 44-item measuring satisfaction with CGM over the previous 6 months. The survey has a high degree of validity ($a \geq 0.94$) in adults with type 1 diabetes using CGM.[31] Several items will be modified for application in healthcare workers. All MICU staff nurses (N=152) will be informed of the study and invited to participate via email. Upon e-consent, the questionnaires will be administered via a REDCap survey. A focus group will be conducted among MICU staff nurses (N=10) to gage their experience using CGM. A semi-structured interview guide will focus on areas of perceived CGM implementation support and education, CGM knowledge, and recommendations for future best practice. All Aim 2 variables and measures appear in Table 2.

RQ 3: To assess glycemic control among patients receiving CGM in the CGM enabled MICU compared to historical control patients who received POC glucose monitoring in the MICU.

Rational/Approach. We will analyze glycemic control factors among MICU patients on CGM compared to 100 historical control patients from the same MICU who receiving only POC glucose monitoring. We hypothesis that patients with CGM will exhibit greater time in range (100-180 mg/dl, 70-180mg/dl, 140-180mg/dl) and experience less frequent time in hypoglycemia than patients on fingerstick POC.

Procedures. Glucose data will be directly transferred from the MICU patients (N=100) to Android mobile phones/Dexcom G6 app which captures and stores glucose values every 5 minutes (up to 288 values/day for 100% CGM wear). CGM data is automatically transferred from phones/Dexcom G6 app to Dexcom Clarity. Individual patient discrete data will be downloads directly from the Clarity site. Historical controls meeting the gateway criteria (glucose >250mg/dl or on IV insulin during admission) from the same MICU will be matched on the following factors: Diagnosis and type of diabetes, home insulin use, steroid use during hospitalization, vasopressor use, North vs. South MICU wings (NP team floor vs. resident team floor, respectively), and diabetic ketoacidosis (DKA)/hyperosmolar hyperglycemic syndrome (HHS) status. POC glucose values for historical controls (N=100) will be obtained directly from OSUWMC EHR. EHR data will be obtained through an information warehouse request providing time stamped, POC glucose value for each match patient. All data will be uploaded into STATA 15.0 where it will be cleaned and merged prior to analysis.

Variables and Measures. Demographic, admission, and diabetes specific variables of interest appear in Table 2 and will be collected from the EHR for MICU participants and for historical controls. Clinical condition variables will include presence of renal replacement, mechanical ventilation, ECMO, associated cardiac arrest or cerebrovascular accident and SOFA score. SOFA score was calculated, though noted to have limited discriminant function for predicting mortality.[32] The SOFA score has been validated in critically ill patients[33], and is currently the scoring system recommended by the Sepsis 3 definition.[34] CGM and POC glucose data will be aggregated into glucose ranges and thresholds as described in Table 2.

Exploratory aim:

RQ 4: To assess hospitalization outcomes and conduct economic evaluation of the costs to deliver CGM implementation in the MICU.

Rational/Approach. We will explore the impact of CGM therapy using a CGM + POC protocol on patient hospital outcomes and costs. Analyzes the economic aspects inpatient CGM on patient health and healthcare interactions, with a focus on the costs (inputs) and consequences (outcomes) of CGM will enable full understanding of implementation effects. We hypothesize that patients with CGM will experience shorter length of stay, lower cost of stay, will be more likely to discharge to home vs. SNF, have a lower 30-day readmission rate, and experience lower mortality/morbidity than matched patients receiving fingerstick POC.

Procedures. Data will be retrospectively extracted from the EHR for patients using CGM in the MICU (N=100) along with 100 historical controls. Data will be obtained from the EHR and billing department through an information warehouse request. Data from the time in motion study will be evaluated to extrapolate the economic impact of nursing personnel time spent for CGM vs. POC glucose monitoring and resources used in POC vs. CGM glucose monitoring.

Variables and Measures. *Hospital outcomes criteria* include the following: Length of stay [ICU, total stay], cost of stay, discharge level of care [home, SNF], morbidity, mortality and readmission rate at 30 days. We will conduct economic evaluation of the costs to deliver CGM implementation in the MICU. We will track resources needed for CGM implementation including personnel, training, facilities, materials, equipment, and other necessary inputs. In addition to resources used, we will expand analysis to evaluate nursing productivity and burden. *Resource outcomes criteria* include: nursing time spent in CGM vs. POC glucose monitoring and cost of CGM vs. standard POC glucose monitoring materials.

Table 2. Patient Participant Schedule of Activities

Aim	Concept	Variable	Frequency	Measure
Aim 1	Clinical utility criteria	Time to CGM validation (Aim 1 only)	Sensor placement (Q10 days)	• EHR • Clarity download
		Mean percent of dosing decisions determined by CGM	Daily	
		Changes in insulin dosing from guideline or outside standard times in response to alarm and/or trend data	Daily	
Aim 1	Fidelity & Adoption Implementation criteria	Proportion of times CGM initiated or patient approached for study inclusion according to protocol/total number of initiations	Admission	• EHR • Study recruitment log
		Proportion of patients approached to received GCM monitoring/number of patients eligible to receive initial CGM monitoring	Admission	
		Acceptability of CGM		
		Appropriateness of CGM		
		Feasibility of CGM		
		CGM knowledge		
Aim 3	Patient condition	Demographic data: Age, race/ethnicity, gender	Admission	• EHR
		Height, weight, and BMI	Admission	
		Diagnosis and type of diabetes	Admission	
		Home diabetes regimen	Admission	
		Total daily insulin dose	Daily	
		Past medical history: tobacco use, COPD, hypertension, heart failure, coronary artery disease	Admission	
		Clinical condition: Admission/inpatient glucose, HbA1c, admission diagnosis, admitting service, MICU	Admission	

		location (North vs. South), DKA/HHS, sepsis, acute liver failure, acute heart failure		
		Clinical condition: SOFA score, dialysis, thromboembolic events, ECMO mechanical ventilation, ICU/hospital length of stay, cardiac arrest, cerebrovascular accident, mortality	Daily	
		Medications: vasopressor use, steroids, anticoagulants, acetaminophen dose	Daily	
		Creatinine, eGFR, ALT, AST, TBR, WBC, procalcitonin, ferritin, CRP, IL6, D-dimer, PTT, INR, troponin, pH, BHB, bicarbonate	Daily	
		Enteral or parenteral nutrition	Daily	
		O2 sat, pAO2, blood pressure	Daily	
Aim 3	Glycemic control	Time in target for CGM patients (70-180mg/dl)	Daily	• Clarity • EHR
		Time 100-180mg/dl for CGM patients	Daily	
		Time 140-180mg/dl for CGM patients	Daily	
		Time above range for CGM patients (>180mg/d & >250mg/dl)	Daily	
		Time in hypoglycemia for CGM patients (<70mg/dl & <55mg/dl)	Daily	
		Percent POC in target (70-180mg/dl) (matched controls)	Daily	
		Percent POC 100-180mg/dl (matched controls)	Daily	
		Percent POC 140-180mg/dl (matched controls)	Daily	
		Percent POC above range (>180mg/dl & >250mg/dl) (matched controls)	Daily	
		Percent POC in hypoglycemia (<70mg/dl & <55mg/dl) (matched controls)	Daily	
		Glucose standard deviation	Daily	
		Glucose coefficient of variation	Daily	
Aim 4	Hospitalization outcomes and costs	Length of stay [ICU, total stay]	Discharge	• EHR • Clarity download
		Cost of stay	Discharge	
		Discharge level of care [home, SNF]	Discharge	
		Morbidity	Discharge	
		Mortality	Discharge	
		Readmission rate [30 days]	30d s/p discharge	
		Cost of CGM vs. standard POC glucose monitoring materials.	Discharge	

Table 3. Nurse Participant Schedule of Activities

Aim	Concept	Variables	Frequency	Measure
Aim 2	Nursing care delivery factors	Evaluation of CGM support	Once	• Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) • CGM Satisfaction Questionnaire • Focus groups

Data Management. All data will be labeled with unique identifiers for subject and study, date and time-stamped, and secured in locked filing cabinets in the project office, if hardcopy, on a server housed in a 24/7 offsite university-run networking facility, via web-based data capture, REDCap. To facilitate the HIPAA compliant remote monitoring of CGM data, dummy clinical Clarity accounts will be created for each device/patient. Android phone set-up requires entry of individual Dexcom Clarity account information on each phone.

D. Data Analysis

Descriptive statistics of central tendency (range, mean, median, and standard deviation) will describe variable characteristics and examine data distribution for normality and outliers. Descriptive statistics will summarize the sample characteristics and distribution of each variable. Data will be screened for normality, outliers, and homogeneity. Continuous variables with normal distribution will be reported as mean (standard deviation) while non-normal distribution will be reported as median (interquartile range). For ***RQ1***, multivariate linear models will be used to evaluate clinical utility and implementation variables while examining the effects of patient condition (i.e., sequential organ failure assessment (SOFA) score, renal replacement, ventilator support, pH) as covaries. For ***RQ 2***, For qualitative analysis of focus group data, a code book will be developed a priori based on the semi-structured interview questions. Interview data, fieldnotes and memos were imported into NVivo 12.0 (Doncaster, Australia) for data management and analyzed using a qualitative descriptive approach.[35,36] Two researchers (Faulds and McNett) will perform qualitative analysis. Portions of text will be coded with terms that were low inference ("data close"); then grouped into thematic categories and subthemes.[35] For **RQ3,** hyperglycemic and hypoglycemic events will be identified for CGM and non-CGM users. Discrete CGM glucose values will be used to aggregate derived measures of glucose variability, including time in target (blood glucose value of 70-180mg/dl), time 100-180mg/dl (representing a more conservative target used inpatient), time 140-180mg/dl (representing institutions IV insulin guideline glycemic target), time above target (>180mg/dl & >250mg/dl), time in hypoglycemia (<70mg/dl & <55mg/dl), glucose standard deviation, and coefficient of variation. Daily percent time in target as well as cumulative time in target will be assessed. Time in target will be derived from ADA glucose targets defining hypoglycemia as a blood glucose less than 70mg/dl and peak post-prandial glucose as <180mg/dl [37]. The blood glucose range of 70-180mg/dl is consistent with other studies examining time in target.[38-41] Measures of hypoglycemia will be in accordance with ADA recommendations for measurement at <70mg/dl and <55mg/dl which is a marker of severe hypoglycemia.[42] Days with ≥70% CGM percent wear, as recommended by ADA, will be included in daily time in target analysis.[42] For matched historical control patients, percent POC in target (70-180mg/dl), 100-180mg/dl, 140-180mg/dl, percent POC >180mg/dl and percent POC >250mg/dl, percent POC <70mg/dl and percent POC <55mg/dl will be evaluated consistent with other recent studies.[43,44] For CGM daily glycemic control (i.e., time in range [70-180mg/dl], time 100-180mg/dl, time 140-180mg/dl), linear mixed effect modeling (LMM) for repeated measures will be used to adjust for between subject and within subject variance. A 3-tiered LMM will be used to control for patient, unit, and nurse specific variability. LMM will be repeated for analysis of daily POC glucose control for matched historical control patients for days with ≥3 POC fingersticks performed. Two-sided significance level of 0.05 was used for all the statistical tests. For **RQ4**, the cost analysis for the proposed study will be conducted from the provider perspective. Cost estimation involves three major steps: (1) identify the relevant cost items; (2) measure the use of resources; and (3) place a value on the resources used. We will obtain estimated costs for proposed CGM implementation. Direct benefits and savings tend to fall into one of two categories: either savings from enhanced efficiency and productivity, or savings from outcomes improvement (e.g., reducing length of stay, lower 30 day readmissions). Costs that do not vary with the number of patients will be categorized as fixed costs, whereas those that vary by the number of patients will be defined as variable costs. The costs of the CGM implementation will be compared to costs under a control scenario. We will estimate the potential costs and cost savings resulting from the CGM implementation.

IV. Regulatory and Safety Monitoring

A. OSU Center for Clinical and Translational Science Regulatory Oversight.

The OSU Center for Clinical and Translational Science (CCTS)-Regulatory Knowledge and Support Core assigned Data Safety Monitoring Board (DSMB) will oversee safety activity of the study. The DSMB will have expertise in either the scientific field of study, clinical trials, statistics, research ethics and/or epidemiology as is required of the study. The DSMB will review protocol-specific reports (Enrollment logs; device accountability logs; adverse event logs) created by the research team. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the type, frequency, attribution, severity, seriousness and expectedness of adverse events. An interim

analysis of study results may be performed and source documents void of any identifiers, may be reviewed to allow the DSMB to independently judge whether the overall integrity and conduct of the protocol remain acceptable. The DSMB will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

In providing oversight for the conduct of this study, the DSMB will meet at a minimum of every 6 (six) months during the 2 (two) -year study to review all salient study information. Additional meetings may be scheduled as determined by the DSMB. The boundary for excess harm will equal an observed excess harm which in the judgment of the DSMB, is excessive. All serious adverse events regardless of severity, attribution and/or expectedness will be reported to the DSMB and the OSU Institutional Review Board(IRB) in accordance with their reporting guidelines. The DSMB recommended actions and all pertinent regulatory information will be forwarded to the Food and Drug Administration (FDA) appropriate Institutional Review Board(s), and Sponsor as appropriate.

B. Medical Device Accountability

The devices will be provided to OSU with permission to be used in this study by Dexcom LLC. They are stored at OSU College of Nursing in a locked office dedicated to the study research team. Accountability of devices used will be maintained in a device accountability log that includes device identification (transmitter serial number, sensor serial number, android phone serial number), patient ID; date of initial CGM device placement, date of sensor replacement (if applicable), date range for use. Transmitter, sensor, and phone serial numbers will be linked to participant/patient in the study. Dummy clinical Clarity accounts will be created for each device/patient. Android phone set-up requires entry of individual Dexcom Clarity account information on each phone. The patient's hospital identification label will be placed on the back of the Android phones once the device is placed to correctly match CGM device to the correct patient participant. CGM device orders from the manufacturer (Dexcom, LLC) will be tacked with date of receipt and shipping logs. Dexcom Expiration dates will be checked on initial receipt of items, monthly, prior to delivery to MICU, and prior to patient placement.

C. Adverse Events and Serious Adverse Events

Definition of Serious Adverse Events (SAE)
All temporal medical events will be tracked by the study team. An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, prolongation of existing hospitalization or transfer to a more acute care environment, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or prolong hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical intervention to prevent one of the outcomes listed in this definition.
Severity of Event

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

Relationship to Study CGM
Potential adverse events (AEs) will be evaluated to determine their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical

judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

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

Historically, few adverse events have been reported with Dexcom G6 CGM systems and have been isolated to mild skin irritation associated with the manufactures adhesive.[45]

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Participants are recruited from the MICU and are critically ill. Participants are not excluded based on the severity of critical illness and it is not uncommon for patients to deteriorate in the natural course of treatment or illness. If the study participant's condition deteriorates for reasons related to the study intervention (e.g., hypoglycemia) at any time during the study, it will be recorded as an AE.

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

Adverse Event Reporting

Serious Adverse Event Reporting

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the reviewing Institutional Review Board (IRB) and the manufacturer as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

D. Unanticipated Problems

Definition of Unanticipated Problems (UP)
This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the CGM intervention, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).]

Unanticipated Problem Reporting
The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

E. Study and individual participant stopping criteria:

We plan to enroll participants in waves of 20 with ongoing analysis between waves. We plan to stop the study for the following conditions in consultation with the data safety monitoring board assigned to oversee safety activities and the study:

- Failure to meet initial validation criteria within 24 hours in 20% of participants
- CGM-meter pairs obtained during routine monitoring following initial validation without a change in clinical status prompting hourly monitoring meeting the following criteria:
    - Failure to detect clinically significant hypoglycemia (≥ 2 episodes): CGM value >100 mg/dl with no Urgent Low Soon alert while POC BG <70 mg/dl
    - Failure to detect severe hyperglycemia (≥ 2 episodes): CGM value <180 mg/dl when POC BG >400 mg/dl
    - Inappropriate treatment (≥ 2 episodes): CGM value triggers the opposite action than the POC BG value (CGM >180 mg/dl while POC BG <70 mg/dl or vice versa).
- ≥ 2 episodes of inappropriate insulin dose resulting in clinically significant hypoglycemia (glucose <55mg/dl) after initial sensor validation
- ≥ 2 episodes of iatrogenic DKA (pH <7.3 or serum bicarbonate <15 mEq/L in the setting of elevated ketones) or hyperosmolar nonketotic state (osmolality ≥320mOsm/kg with BG >600mg/dl and pH >7.3 or serum bicarbonate >15 mEq/L)
- ≥ 2 episodes severe adverse events resulting in prolonged hospitalization, or other life-threatening complication that are attributed to the study intervention
- Any severe adverse event resulting in death, or other life-threatening complication that is attributed to the study intervention
- Any severe adverse event resulting in prolonged hospitalization, or other life-threatening complication that attributed to the study intervention and is expected to recur

Patient participation in the study will stop if any of the following occur:

- Failed sensor validation x 2 sensors (48 hours)
- Transitioned to hospice care
- Patient participant or patient's legally authorized representative withdraw consent

Appendix A. Device label

CAUTION Investigational Device. Limited by United States Federal law to investigational use

Dexcom G6 Continuous Glucose Monitoring System (CGM)

Manufacturer: Dexcom LLC, 6340 Sequence Drive
San Diego, CA 92121, USA
Package contains: 1 sensor, 1 transmitter, 1 android phone

Dexcom G6 CGM may fail to adequately detect high (hyperglycemia) or low (hypoglycemia) glucoses which could result in adverse events including death. High dose acetaminophen (>1 gram Q6 hours) or treatment with hydroxyurea may interfere with device accuracy. May not be worn during magnetic resonance imaging (MRI), computerized tomography (CT) radiographic procedures, or diathermy.

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