**PROTOCOL TITLE: Randomized Controlled Trial To assess the Benefits of Dexcom Continuous Glucose Monitoring with Glucose telemetry System for the Management of Diabetes in Long-term Care Setting: The CGM-GTS in Long-term care**

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**Short Title:** Dexcom CGM in Long-term care

**Funding Source:** Dexcom, Inc

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## 1. Study Summary

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|---|---|
| **Study Title** | Randomized Controlled Trial To assess the Benefits of Dexcom Continuous Glucose Monitoring with Glucose telemetry System for the Management of Diabetes in Long-term Care Setting: The CGM-GTS in Long-term care |
| **Study Design** | Randomized Controlled Trial |
| **Primary Objective** | To compare differences in frequency of hypoglycemia (<70 mg/dl) and glycemic control (time in range [TIR] 80-180 mg/dl) between the Dexcom CGM with Glucose Telemetry System (CGM-GTS) compared to a standard of care protocol, in residents with T2D treated with insulin and/or insulin-secretagogues, in subacute and long-term skilled nursing care facilities. |
| **Secondary Objective(s)** | Determine differences in clinical outcomes (number of complications, ER visits and need for hospital re-admissions), and health care utilization between the use of real-time Dexcom CGM Glucose Telemetry System (CGM-GTS) compared to a standard of care in patients with T2D in subacute and long-term skilled nursing care facilities. |
| **Research Intervention(s)/Interactions** | POC testing or to real time Dexcom CGM with GTS for up to 60 days of admission. |
| **Study Population** | Adult residents with T2D in subacute and long-term skilled nursing care facilities treated residents with T2D treated with insulin and/or insulin-secretagogues. |
| **Sample Size** | 100 |
| **Study Duration for individual participants** | Length of admission to subacute and long-term skilled nursing care facilities or up to 60 days (whichever comes sooner) |
| **Study Specific Abbreviations/ Definitions** | **T2DM**: Type 2 Diabetes Mellitus<br>**OADs**: oral antidiabetic medications<br>**CGM**: continuous glucose monitor<br>**GTS**: glucose telemetry system<br>**LTC:** Long Term Care<br>**SSI:** Sliding Scale Insulin |
| **Funding Source (if any)** | Dexcom, Inc. |

## 2. Objectives

Diabetes is common in patients in subacute and long-term skilled nursing care facilities. Most patients with T2D are treated with insulin alone or in combination with oral antidiabetic agents, with reported high rate of iatrogenic hypoglycemia [12,13]. The rate of hypoglycemia in sulfonylureas and insulin treated patients is reported ~ 30-40%, and the development of hypoglycemia has been associated with greater resource utilization and higher emergency room and hospital transfers compared to residents without hypoglycemia [44]. The use of CGM has been shown superior to POC testing (standard of care) in detecting both hypo- and hyper-glycemic events [21]. The use of CGM with glucose telemetry system (CGM-GTS) with alarm reduces the frequency and time in hypoglycemia compared in insulin treated patients with T2D compared to POC. We propose to conduct a RCT to compare the efficacy of CGM-GTS in reducing hypoglycemia in high risk population with T2D treated with insulin and/or insulin-secretagogues in subacute and long-term skilled nursing care facilities

## 3. Background

**Prevalence of diabetes in older adults and subacute and long-term skilled nursing care facilities.** The prevalence of diabetes increases with age, and it is estimated that more than 20% of older adults aged 65-75 years and 40% of adults >80years of age have diabetes[29,30]. The prevalence of diabetes in older adults is expected to increase due to longer life expectancy and improve care of the population[30,31]. The estimated prevalence of diabetes in subacute and long-term skilled nursing care facilities is reported to be ~ 20% to 34%[1], and in parallel to the increasing geriatric population, the number of LTC admissions is expected to rise[31].

**Diabetes treatment in LTC facilities.** The goals of diabetes care in older adults and in patients in subacute and long-term skilled nursing care facilities include control of hyperglycemia and its symptoms, prevention and treatment of diabetic complications, and maintenance or improvement of general health status. Studies in hospitalized patients with diabetes have shown that improvement in glucose control can reduce complications and are cost savings[7,18,32]; however, no prospective studies have determined the impact of improving glucose control on clinical outcome in subacute and long-term skilled nursing care facilities (LTC). The management of diabetes in LTC residents is similar to that recommended for ambulatory patients with diabetes[33,34]; however, several factors complicate the management of hyperglycemia in this population[8]. LTC residents tend to be older and to have higher rates of comorbidities associated with aging such as functional disability, hypertension, coronary artery disease, cerebrovascular events, depression, cognitive impairment, urinary incontinence, and higher risk of falls. In addition, they often experience changes in nutritional intake, which increase the risk of hypoglycemia[5-8].

**Current guidelines and position statements on diabetes management in older adults** [35-38] are based on consensus opinions or from extrapolations from studies involving middle-aged patients with diabetes. The American Diabetes Association guidelines recommend that older adults who are functional, cognitively intact, and have longer life expectancy should receive diabetes care with goals similar to those developed for younger adults [36]. In these subjects, a

HbA1c level <7.5%, a fasting glucose between 90-130 mg/dl, and a random glucose <180 mg/dl is recommended. Less intensive goals are recommended for patients with advanced complications, life-limiting comorbid illness, or cognitive impairment. Other organizations including the American Geriatric Society, European Diabetes Working Party for Older People guidelines, International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People recommend a target HbA1c of <7.5% for patients without major comorbidities while a higher target of 7.6-8.5% is proposed for frail patients with high risk of hypoglycemia[35,39-44]. These guidelines highlight the importance of improved glucose control and avoidance of side effects and hypoglycemia, as they are associated with increased risk of complications and mortality in patients with diabetes[40-44].

**Diabetes drug utilization in subacute and long-term skilled nursing care facilities (LTC).** There are twelve antidiabetic drugs with different mechanisms of action to treat patients with T2D[45]. Metformin is recommended as first choice OAD agent for the management of patients with T2D[36,46]; however, it may cause anorexia, nausea, diarrhea, weight loss, and lactic acidosis in patients with impaired renal function[47,48]. Insulin secretagogues are effective in reducing glucose levels, but are associated with high risk of hypoglycemia[49]. Thiazolidinediones improve insulin sensitivity but frequently cause weight gain, edema, osteopenia and are contraindicated in subjects with heart failure[49,50]. The α-glucosidase inhibitors delay carbohydrates absorption, but are associated with a high rate of GI side effects[48]. DPP4-inhibitors are promising agents in the elderly because they stimulate insulin secretion in a glucose-dependent fashion, thus not causing hypoglycemia when used as monotherapy or in combination with metformin therapy[51-53].

Insulin therapy is widely recommended for diabetes management in LTC residents [54,55]. Recent reports indicate that prescribing pattern in patients with diabetes in LTC facilities is shifting towards insulin, accounting for nearly 68% of new drug starts [56]. Clinical guidelines recommend initiating insulin when oral agents fail or are contraindicated, and when random BG levels are >180 mg/dL[54,55]. These guidelines favor the use of basal bolus insulin regimens over sliding scale regular insulin[57-59]. The basal bolus insulin has been shown to improve glycemic control [60-62] and to reduce hospital complications in patients with T2D[62]; however, insulin administration approach is associated with high risk of hypoglycemia (see preliminary results).

**Glucose monitoring in subacute and long-term care settings: Capillary point of care (POC) and CGM glucose testing.** Bedside capillary POC glucose monitoring is the standard of care to assess glycemic control in the hospital and in LTC facilities [17-19]. POC testing is usually performed before meals and at bedtime. CGM measures interstitial glucose every 5-15 minutes, thus provides a more complete glycemic profile during 24-hours than POC testing. Several randomized trials have shown that CGM systems facilitate and improve diabetes care in insulin-treated ambulatory patients [63-65], as well as in hospitalized patients [21,23,66-69]. In a recent study of hospitalized patients with T2D, we reported increased detection of both hypo- and hyper-glycemic events with the use of CGM compared to the standard-of-care POC BG testing [21]. More than 50% of the hypoglycemic events occurred between dinner and breakfast; suggesting that these episodes would be missed by standard POC testing. In addition, a prospective

hospital study in insulin treated patients with T2D by our group reported that 45% of hypoglycemic events were asymptomatic [70]. In multivariate analysis, male gender (OR 2.08, 95% CI 1.13 to 3.83, p=0.02) and age >65 years (OR 4.01, 95% CI 1.62 to 9.92, p=0.02) were independent predictors of asymptomatic hypoglycemia. A recent panel of experts in inpatient diabetes care reported that CGM could more effectively identify trends toward hypoglycemia and hyperglycemia, allowing for better and safer management of patients with inpatient hyperglycemia [71,72].

Recent reports indicate that CGM data can be transmitted to the nursing station by way of automatic downloading into a monitor at the nursing station. A recently published study evaluated whether the Dexcom CGM using a "Glucose Telemetry System" can decrease hypoglycemia in the general wards/non-ICU setting[92]. The study included insulin treated patients with T2D at high risk for hypoglycemia. Participants were randomized to either the "Glucose Telemetry System" (intervention group) or to POC BG testing (control group). For patients in the "Glucose Telemetry System" nurses were instructed to proceed with hypoglycemia prevention actions if the low glucose alerts were activated (set at <85 mg/dl). Participants in the control group were placed on "blinded" CGM systems which were only used to collect glucometrics data. Overall, the subjects in the CGM-GTS experienced fewer events of hypoglycemia (<70 mg/dL), clinically significant hypoglycemia (<54 mg/dL) compared to the POC BG group. The outcomes of the intervention versus control groups for these two levels of hypoglycemia were, respectively, 0.67 versus 1.69 events/ patient, p =0.024 (< 70 mg/dl) and 0.08 versus 0.75 events/patient, p =0.003 (< 54 mg/dl). In addition, there was a reduction in percentage of time in hypoglycemic range <70 mg/dl and <54 mg/dl in the GTS compared to POC group (0.40%, versus 1.88%, p =0.002 and 0.05%, versus 0.82%, p =0.017). In the current research proposal, we will use the Dexcom G6 CGM with GTS and alarm set up at 85 mg/dL to prevent hypoglycemia.

**Significance and Innovation.**

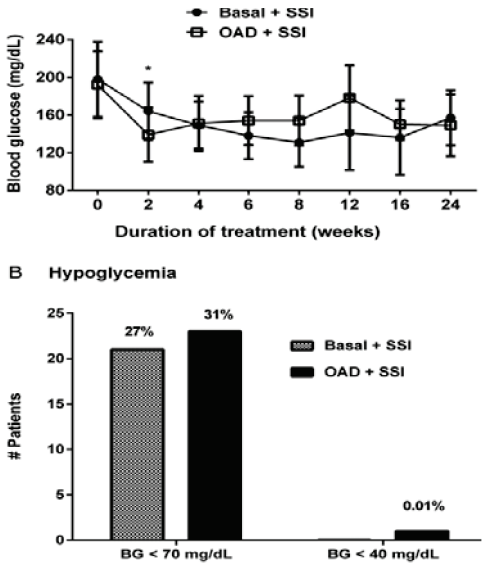
**Significance.** Two previous RCTs in the subacute and LTC facilities comparing oral agents and basal insulin reported similar improvement in glycemic control, but high rates of hypoglycemia in patients treated with basal insulin [12,13]. The rate of hypoglycemia in insulin and sulfonylureas treated patients was 30-40%. Patients with hypoglycemia required greater resource utilization and higher emergency room and hospital transfers compared to residents without hypoglycemia [44]. The high rate of insulin-associated hypoglycemia is worrisome, as recent population studies have suggested that diabetes prescribing in LTC is shifting towards insulin, accounting for ~half of patients with T2D [44] and nearly 68% of new drug starts [56]. Capillary POC glucose testing is the standard of care for glucose monitoring in the hospital and LTC facilities. Our group and others have shown that POC misses about 40% of hypoglycemia cases, particularly at night (REF). Increased detection of both hypo- and hyper- glycemic events have reported with the use of CGM compare to the POC BG [21]. In addition, we recently reported that CGM-GTS with alarm can successfully reduce the frequency and time in hypoglycemia compared in insulin treated patients with T2D compared to POC (REF). We anticipate that by Reducing hypoglycemia in subacute and long-term skilled nursing care facilities may reduce the rate of complications, ER visits and need for hospital readmissions.

***Innovation.*** We propose the first RCT to assess the impact of glucose control and hypoglycemia reduction with the use of real time CGM with an alarm system to prevent hypoglycemia and facilitate the care of insulin and non-insulin treated patients with T2D in subacute and long-term skilled nursing care facilities. The results of this study have great potential to impact and facilitate care and to change current clinical guidelines in the management of older adults with diabetes in subacute and LTC facilities.

**PRELIMINARY RESULTS:**

**Diabetes and Clinical Outcome in LTC Residents** [44]. In a retrospective study, we analyzed the quality of diabetes care, glycemic control, and clinical outcome in 1,409 subjects admitted to 3 community LTC facilities in Atlanta. The prevalence of diabetes was 34.2%. On admission, patients with diabetes were sliding scale regular insulin (25%), OADs (5%), insulin (34%), or with combination of OADs and insulin (26%). Patients with diabetes had higher number of complications and required more emergency room and hospital transfers. A total of 42% of patients had ≥ 1 episode of BG <70 mg/dl and 7% had a BG <40 mg/dl. Hypoglycemia was reported in 45% on OADs (mostly sulfonylurea plus SSI), or insulin therapy. Patients with hypoglycemia had a longer length of stay, higher emergency room or hospital transfers (44% vs. 30%; p=0.004) and higher mortality (18% vs. 10%, p=0.015). These results indicate that diabetes is common in LTC and is associated with higher resource utilization and complications, and that hypoglycemia is associated with increased rates of emergency room care and hospitalization, length of stay, and mortality[44].

Fig 1-Oral agents vs. Basal Insulin in LTC




**Comparing of Oral Antidiabetic Agents and Basal Insulin in LTC Residents with T2D [12].** In a prospective study we recruited 150 patients from 2 university-affiliated facilities with BG > 180 mg/dl or A1C >7.5%, treated with diet and/or with stable dose of OADs or glargine (starting at 0.1 U/kg/day), were randomized to continue OAD plus sliding scale insulin or to basal insulin glargine starting at 0.1 U/kg/day plus SSI for up to 6 months (Fig 1). There were no differences in daily glucose or with the A1C at 3 months or at 6 months or in the number of patients with hypoglycemia (basal 28% vs. control 31%, p=0.37). The results of this study indicated similar improvement in glycemic control, without differences in mean daily BG, hypoglycemia with basal insulin or with OADs and SSI supplements. It was also evident that 1/3 od treated with OADs and insulin experienced hypoglycemia indicating the need for safer regimens.

**DPP4-inhibitors vs Basal insulin in LTC (Linagliptin-LTC Trial)[13].** A 6-month open-label pilot randomized controlled trial compared the efficacy and safety of a DPP4-i (linagliptin) and basal insulin in subacute and LTC residents with T2D admitted to 3 institutions affiliated with Emory University. A total of 140 residents with T2D treated with oral antidiabetic agents or low-dose insulin (0.1 U/kg/d), with fasting BG>180 mg/dL and/or HbA1c >7.5% were randomized to linagliptin 5 mg day or glargine at a starting dose of 0.1 U/kg/d. Baseline antidiabetic therapy, except metformin, was discontinued on trial entry. BG was measured before meals and both groups received supplemental rapid-acting insulin before meals for BG > 200 mg/dL. As shown in Figure 4, treatment with linagliptin resulted in no significant differences in mean daily BG, but resulted in fewer mild hypoglycemic events <70 mg/dL (3% vs. 37%, P <0.001), and a non-significant trend towards lower risk of BG <54 mg/dL (0% vs 7%, p=0.06). There were no significant between-group differences in length of stay, complications, emergency department visits, or hospitalizations. These results suggested that DPP4-inhibiors are effective and represent an alternative to insulin therapy in many LTC residents with T2D.

Fig 2- Linagliptin vs Basal Insulin in

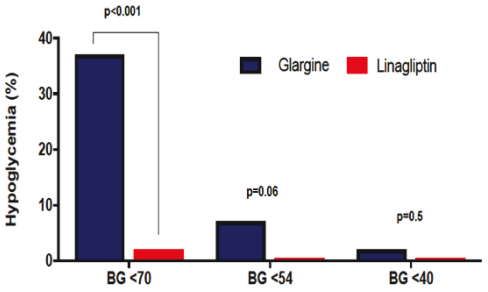



**Fig 3. Hypoglycemia by POC and CGM**

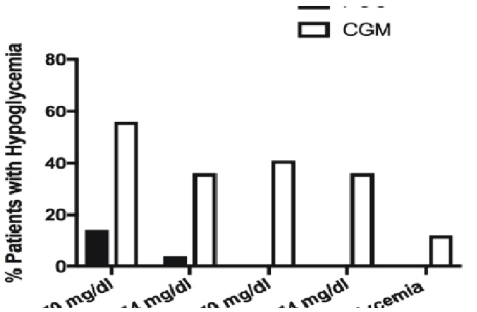
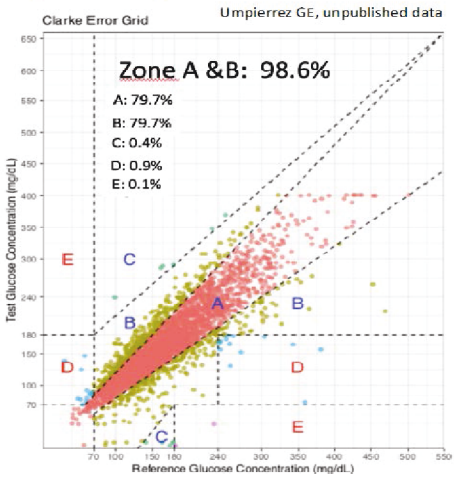



**Fig 4. Accuracy Dexcom G6 in T2D, n=20a5**

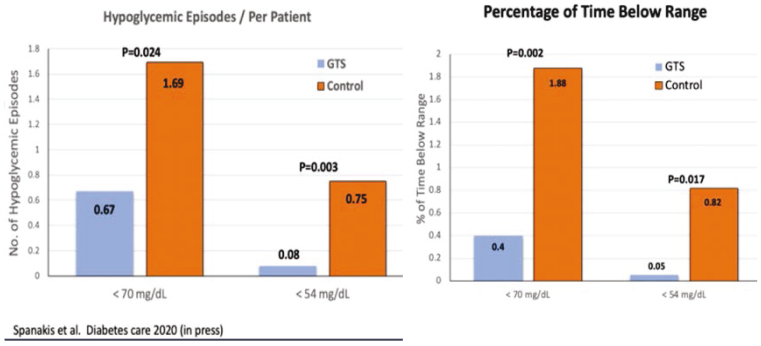
**Continuous glucose monitoring (CGM) in the hospital setting.** Our research team have reported on 3 RCTs comparing the accuracy of using of CGM and capillary point of care (POC) glucose testing in insulin treated patients with T2D [21,24,73,74]. Increased detection of both hypo- and hyper-glycemic events with the use of CGM compared to POC testing was found. More than 50% of the hypoglycemic occurred at night; suggesting that many of these episodes would be missed by standard POC testing. In a recent study [24], we compared the performance of the FreeStyle Libre Pro CGM and POC glucose testing among insulin-treated hospitalized patients with T2D. The mean daily glucose was higher by POC testing, and proportions of patients with BG <70 mg/dl and <54 mg/dl by POC BG were lower compared to CGM, all p<0.001 (Fig 3). The overall mean absolute relative difference (MARD), the statistical measure of accuracy used as the standard in glucose monitoring to represent performance, was 14.8%, ranging between11.4 to 16.7% for glucoses between 70 and 250 mg/dl and the Error Grid analysis showed 98.0% of glucose pairs within Zones A and B.




In Figure 4, we present the accuracy of the Dexcom G6 CGM compared to POC testing in 218 consecutive insulin-treated general medicine (n= 192) and surgery (n= 26) patients with T1D (n= 9) and T2D (n=209). The mean age was 61 ±12 years, HbA1c 9.07±2.2%, admission BG 224±2 mg/dl, with 47% of patients with eGFR < 60 ml/min, length of stay, median 5.0 (4.0, 10.0) days. The Overall mean absolute relative difference (MARD) was 12.692 and median ARD of 10.048

during the hospital stay and with 98.6% of matched pair readings within Error Grid within Zones A and B (Figure 4).

**Real Time CGM with Glucose telemetry System.** We have conducted several clinical studies with GTS to transmit CGM data to the nursing station. A recently published study evaluated whether the Dexcom CGM using a "Glucose Telemetry System" can decrease hypoglycemia in the general wards/non-ICU setting92. This report is the first interventional RCT study of CGM to improve outcomes in the non-ICU setting. The study included patients with T2DM, who were at high risk for hypoglycemia. Participants were randomized to either the "Glucose Telemetry System" (intervention group) or to POC BG testing (control group). For patients in the "Glucose Telemetry System" nurses were instructed to proceed with hypoglycemia prevention actions if the low glucose alerts were activated (set at <85 mg/dl). Participants in the control group were placed on "blinded" CGM systems which were only used to collect glucometrics data. Overall, the subjects in the CGM-GTS experienced fewer events of hypoglycemia (<70 mg/dL), clinically significant hypoglycemia (<54 mg/dL) compared to the POC BG group. The outcomes of the intervention versus control groups for these two levels of hypoglycemia were, respectively, 0.67 versus 1.69 events/ patient, p =0.024 (< 70 mg/dl) and 0.08 versus 0.75 events/patient, p =0.003 (< 54 mg/dl). In addition, there was a reduction in percentage of time in hypoglycemic range <70 mg/dl and <54 mg/dl in the glucose telemetry system group compared to POC group (0.40%, versus 1.88%, p =0.002 and 0.05%, versus 0.82%, p =0.017).




**Summary of Preliminary Data:** The result of studies demonstrates that hypoglycemia is common in insulin and non-insulin treated patients admitted to subacute and LTC facilities. Most of these episodes are missed when using capillary POC testing, with CGM providing a more complete assessment of glycemic status, detecting episodes of diurnal and nocturnal hypoglycemia compared to POC testing. The accuracy of Dexcom G6 is excellent and used together with GTS, reduces the frequency and time in hypoglycemia. The proposed RCT have great potential to impact and facilitate care of patients with diabetes in subacute and long-term LTC facilities, and might change current clinical guidelines in the management of patients with diabetes in subacute and long-term skilled nursing care facilities.

## 4. Study Endpoints

Diabetes is highly prevalent among adults admitted to subacute and long-term skilled nursing care facilities (LTC) 1-4. Management of diabetes in these LTC facilities is challenging due to number of older adults with high prevalence of comorbidities, functional disability and altered nutritional intake, which increase the risk of hypoglycemia5-8.
Clinical guidelines from professional organizations 9-11 recommend the use of subcutaneous insulin, as the preferred therapy for glycemic control for most patients with type 2 diabetes (T2D) in LTC facilities. Although effective in improving glycemic control, observational and prospective randomized studies have reported rates of hypoglycemia between 30-37% with insulin administration in LTC residents with T2D 12,13. The high frequency of hypoglycemia is of great concern, as it has been associated with cardiac complications, emergency room visits, hospital admissions and mortality 14-16.

Bedside capillary point-of-care (POC) glucose monitoring is the standard of care to assess glycemic control in the in LTC facilities 17-19. POC testing is recommend by national guidelines before meals and at bedtime. This approach provides limited evaluation of glycemic excursions and to miss nocturnal hypoglycemia 20-23. Continuous glucose monitoring (CGM) measures interstitial glucose every 5-15 minutes, thus providing a more comprehensive 24-hours glycemic profile assessment than POC testing.

Recent studies from our group and others in hospitalized patients with T2D have reported increased detection of both hypo- and hyperglycemic events with the use of CGM compared to POC BG testing 21,23-25. We also reported that the hospital use of the Glucose Telemetry System with Bluetooth technology allows CGM glucose values to be transmitted from the patient's bedside to a central monitoring device in the nursing station, reducing the frequency of hypoglycemia in insulin treated patients with T2D 26,27. More recently, in collaboration with the University of Maryland, reported significant reduction in the rate of hospital hypoglycemia in insulin treated medicine and surgery patients with T2D using the glucose telemetry system with real-time CGM 28. In addition, the use of Dexcom G6 CGM in insulin-treated patients revealed great accuracy, with 98.6% of reading within Clarke error Grid A and B (unpublished data, see preliminary results section). Thus, our experience in the hospital supports the use of the use of CGM for the management of patients with diabetes and prevention of hypoglycemia. However, we do not know if this experience can be extrapolated to individuals in long-term skilled nursing facilities. Therefore, in-depth analyses of glycemic control and potential benefit of RT-CGM in real-world is needed to determine whether the CGM-GTS can improve glycemic control and prevent hypoglycemia in vulnerable population of adult patients admitted to LTC facilities.

<u>The primary aim</u> is difference between POC testing and CGM-GTS in the frequency of hypoglycemia (safety outcome) and glycemic control (efficacy outcome) during admission.

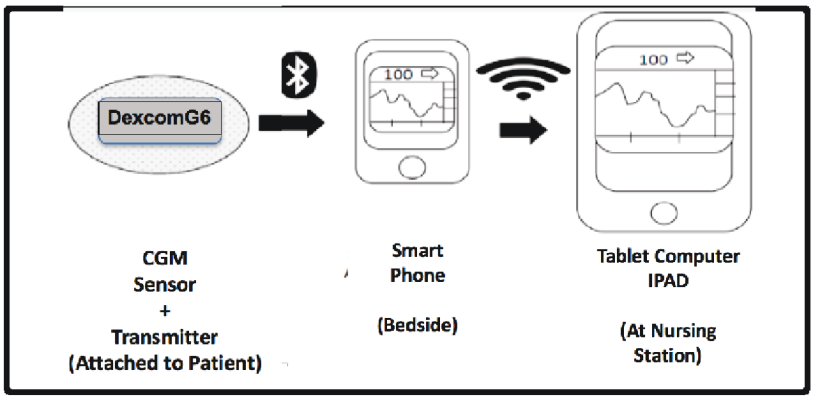
1) Hypoglycemia <70 mg/dl and clinically significant hypoglycemia <54 mg/dl (safety outcome)
2) Glycemic control, as measured by time in range (TIR) between 80-180 mg/dl (efficacy outcome)

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

1. Nocturnal hypoglycemia < 70 mg/dl and < 54 mg/dl (between 22:00 and 06:00)
2. Number of hypoglycemia events (< 70 and 54 mg/dl)
3. Time in hypoglycemia (<70 mg/dl) and hyperglycemia (>240 mg/dl)
4. Number of prolonged hypoglycemia > 1 and 2 hours by CGM
5. Frequency and time of hypoglycemic during the day and night
6. Frequency and duration or time on hyperglycemia > 240 mg/dl
7. Percentage of BG readings within target BG of 70 and 180 mg/dl
8. Glycemic variability calculated by standard deviation and MAGE
9. Number of sensor removal for procedures/imaging, sensors failures, sensors dislodgments

## 5. Study Intervention/Investigational Agent

We propose to conduct a randomized controlled trial to determine whether compared to standard of care using capillary POC testing, the use of Dexcom CGM with Glucose Telemetry System (CGM-GTS) with hypoglycemia alarm will facilitate diabetes treatment and reduce the risk of hypoglycemia in insulin and non-insulin treated patients with T2D in LTC facilities.

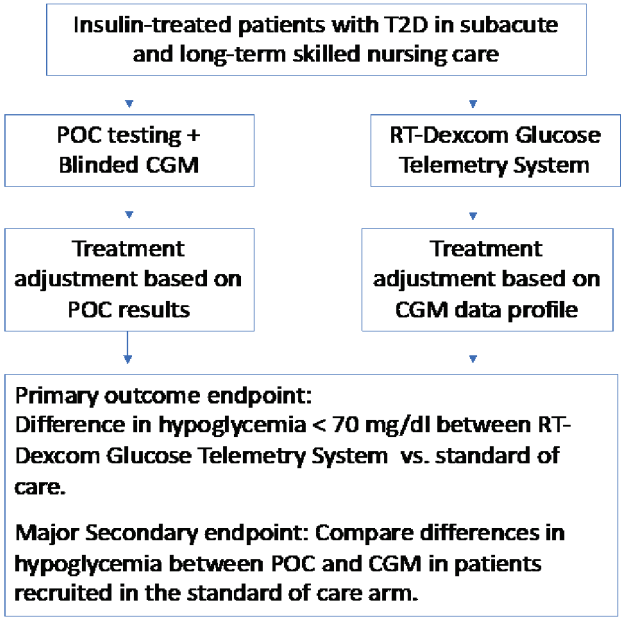



Dexcom CGM- Glucose Telemetry System CGM-GTS). The system will include 3 main devices, i) DEXCOM G6 CGM device (sensor, transmitter, ii) a smart phone, and iii) a tablet computer located at the nursing station. As a first step glucose values obtained from the CGM sensor will be sent to the CGM transmitter by Bluetooth technology and DEXCOM Share2 software application to a smart phone that serves as an intermediate-transmitting (routing) device. The study phone will be locked in a safe box located in the patient's room. With the help of commercial internet wireless network, glucose values from the smart phone will be transmitted wirelessly to a table computer (I-Pad) using the DEXCOM Follow application [https://www.dexcom.com/apps].

## 6. Procedures Involved

Residents with T2D in subacute and long-term skilled nursing care facilities treated with insulin and/or insulin-secretagogues will be randomized to a standard of care group with POC testing or to real time Dexcom CGM with GTS for up to 60 days of admission.

Patients in the standard of care group will wear a blinded CGM and receive POC testing before meals and bedtime, with providers adjusting oral agents or insulin dose based on POC results. Patients in the intervention CGM group will have a single daily fasting POC testing and will wear a real-time Dexcom G6 with GTS, and providers will adjust oral or insulin therapy based on CGM-GTS profile information.




Nursing staff and primary care will receive education on the CGM technology by our research team. Education efforts will include general information on the technology, how and when to remove or replace CGM sensors and transmitters, and the hypoglycemia prevention protocol. Treatment of hypoglycemia (POC <70 mg/dl) will be similar in both groups following a standard hospital protocol.

CGM alarm settings, and prevention of hypoglycemia protocol. Hypoglycemia alarm will be set to < 85 mg/dl (for prevention for low blood glucose levels). Nursing staff will be instructed to provide 15 grams of carbohydrates in response to a hypoglycemia alarm. For control group (blinded CGM) CGM alarms are turned off, however if the POC is found to be between <80 mg/dl by POC, 15 grams of carbohydrates will be given as a preventive measurement for hypoglycemia (standard of care).

The hyperglycemia alarm will be set at 300 mg/dl. If this occurs, the nursing staff will assess clinical status and perform a POC glucose testing to confirm glucose values. If BG > 300 mg/dl, nursing staff will communicate the high glucose value to the primary care team.

**Diabetes Management Protocol**

We will recruit and randomize males and females with a known history of T2D treated with oral antidiabetic agents, short- and long-acting GLP1-RA or insulin therapy. Glycemic target during admission is to maintain BG between 80-180 during the day, while avoiding hypoglycemia < 70 mg/dl.

**Patients treated with oral antidiabetic agents.** Dose of antidiabetic agents will be continued after randomization unless there is contraindication (i.e., eGFR < 30 mil/ml for patients on metformin and SGLT2; pioglitazone and heart failure, history of pancreatitis for DPP4-I or GLP1-RA), or sulfonylurea (eGFR < 30 ml/min or history of severe hypoglycemia). patients will receive

supplemental/correction insulin for BG >200 mg/dL per sliding-scale. The attending physician could adjust oral medications at his/her discretion in the presence of severe glycemic excursions.

**Recommended Insulin staring dose for insulin naïve patients.** If primary care opts to start insulin therapy, the recommended dose of basal insulin is 0.1 unit/kg, given at the same time every day. Dose of oral agents may be continued, but sulfonylurea agents should be reduced by half or stopped to prevent hypoglycemia.

**Patients T2D Treated with Insulin**. Subjects treated with insulin will continue to receive their total daily dose (TDD) and insulin formulation after randomization. Glycemic target during admission is to maintain BG between 80-180 during the day, while avoiding hypoglycemia < 70 mg/dl.

The attending physician could adjust total daily insulin dose following the suggested insulin adjustment protocol:

**Basal Insulin adjustment.**

- Daily basal (glargine, detemir or degludec) insulin dose will be adjusted as follow:
- If the fasting and pre-dinner BG is between 100 - 180 mg/dl in the absence of hypoglycemia the previous day: no change
- If the fasting and pre-dinner BG is between 181 - 250 mg/dl in the absence of hypoglycemia: increase basal insulin by 10% every day
- If the fasting and pre-dinner BG is between 251 - 350 mg/dl in the absence of hypoglycemia: increase basal insulin by 20% every day
- If the fasting and pre-dinner BG is > 350 mg/dl in the absence of hypoglycemia the previous day: increase basal insulin (glargine) dose by 30% every day
- If the fasting and pre-dinner BG is between 70 - 99 mg/dl in the absence of hypoglycemia: decrease TDD (basal and prandial) insulin dose by 10% every day
- If BG <70 mg/dL, the insulin TDD (basal and prandial) should be decreased by 30%.
- If BG <40 mg/dL, the insulin TDD (basal and prandial) should be decreased by 40-50%.

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

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

  BEFORE MEAL, Supplemental Sliding Scale Insulin (number of units) - Add to scheduled insulin dose.

| BG (mg/dL) | |
|---|---|
| < 200 | Do not give extra insulin |
| 201-300 | Give extra 2 units regular insulin |
| 301-400 | Give extra 4 units regular insulin |
| 401-450 | Give extra 6 units regular insulin |
| > 450 | Call NP, PA, or MD |

## 7. Data and Specimen Banking

Not applicable

## 8. Sharing of Results with Participants

The result of instant blood sugar will be shared with patients, nurses and health care providers immediately at LTC. However, the final results of the study and its finding will not be shared with participants.

## 9. Study Timelines

The duration of an individual participant's participation in the study will be equal the length of admission to subacute and long-term skilled nursing care facilities (LTC) or up to sixty (60) days, whichever comes sooner.

## 10. Inclusion and Exclusion Criteria

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

**Inclusion Criteria:**

1. Males and females admitted to subacute and long-term skilled nursing care facilities
2. Known history of T2D treated with insulin (glargine, detemir, degludec, NPH, premixed insulin) or sliding scale regular insulin) or insulin secretagogues (sulfonylureas, repaglinide, nateglinide) with or without additional oral antidiabetic agents (alpha-glucosidase inhibitors, thiazolidinedione, SGLT2- inhibitors, DPP4-inhibitors), short- and long-acting GLP1-RA (exenatide, liraglutide, dulaglutide, semaglutide)
3. Patients with an expected LTC length-of-stay > 1 week

**Exclusion Criteria:**

1. Patients expected to require MRI procedures during admission.
2. Patients with clinically relevant hepatic disease (diagnosed liver cirrhosis and portal hypertension), corticosteroid therapy, end-stage renal disease (dialysis), or anasarca (massive peripheral edema).

3. Female subjects who are pregnant or breast-feeding at time of enrollment into the study.

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

## 11. Vulnerable Populations:

Prisoners, pregnant women, neonates will not be included in the study. Nursing home residents with diabetes have higher rates of serious comorbidities and have greater activity of daily living dependencies than other residents without diabetes. The present study aims to determine *if CGM -GTS* will benefit the management and reduce the risk of hypoglycemia of LTC patients with T2DM. Research staff will ask the primary care team about the resident's cognitive status and ask if they are able to consent. If the primary team deems the patient is not able to give informed consent then we will approach the legal representative *(*durable power of attorney for health care, court appointed guardian for health care decisions, spouse, *or* adult child*).*

## 12. Local Number of Participants

*The total number of participants to be accrued locally is 100.*

## 13. Recruitment Methods

Coordinators will screen for potential participants from the electronic medical record. Once a potential research candidate is identified, the investigators and/or research coordinators will discuss the research protocol with the provider (doctor, nurse, or house staff) taking care of the SAR/LTC resident and request permission to include him/her in the trial. If the primary provider agrees to include the resident in the trial, then he/she will be invited to participate in the study. Subjects will be approached by phone or in their facility room to find out their interested. If the potential candidate is interested, they will be provided with sufficient information on the practice of glucose monitoring before providing written consent. If the primary team deems the resident is not able to give informed consent then we will approach the legal representative (durable power of attorney for health care, court appointed guardian for health care decisions, spouse, or adult child) by phone. In this case, a verbal consent will be obtained, and a full copy of the consent will be provided by email or regular mail. The process of obtaining informed consent will follow the standard procedures of Emory University. This protocol will be submitted for approval by the Emory IRB.

Participation in this study is voluntary. Participants will receive one hundred dollars ($100.00) during the LTC stay. Total compensation will be one hundred dollars ($100).

## 14. Withdrawal of Participants

Participants may withdraw from the study if they decided to. They also will have the right to request that any data was collected to be removed by contacting members of the research team.

## 15. Risks to Participants

**Potential Risk to Human Subjects**

**Hypoglycemia.** The risk of hypoglycemia in patients treated with insulin regimens is between 12%–35% [61,62,79,80]. In this study, hypoglycemia is defined as a BG or IG < 70 mg/dL. Clinical significant hypoglycemia is defined as BG or IG < 54 mg/dl. Severe hypoglycemia is defined as BG < 40 mg/dL.

**Use of CGM.** No major risks are expected with the use of the CGM device. Pain and bleeding with insertion is minimal. Skin irritation may occur in those sensitive to adhesives.

**Protection against Risks**

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor capillary BG at the bedside using a hand-held glucose meter, b) only experienced nurses/or phlebotomist will draw blood samples. To prevent significant clinical events, no patients with history of significant liver, renal impairment or cardiac failure will be recruited in this study.

We expect that approximately 20-30% in insulin and sulfonylurea treated patients will experience one or more episodes of hypoglycemia. To minimize the risk of hypoglycemia, the starting dose will be adjusted following a protocol that has been shown effective on insulin adjustment. To avoid hypoglycemia, the total daily dose of insulin will be decreased by 10% for BG between 70-99 mg/dl and by 20% after each episode of hypoglycemia (BG < 70 mg/dl).

**CGM – alarms and hypoglycemia protocol.** We will use a Dexcom CGM device with a modified transmitter able to store and transmit glucose data to different devices including a notebook/IPAD or computer desk located at the nursing station. The use of hypoglycemia alarm set at 85 mg/dl will alert nursing staff and providers that a patient maybe at risk of hypoglycemia. If this occurs, the nursing staff will meet patient in the room to assess clinical status and signs/symptoms of hypoglycemia and will perform a POC glucose testing to confirm glucose values. In addition, a carbohydrate load of 15 grams will be provided to patients as per hospital protocol to avoid hypoglycemia.

**Hyperglycemia alarm** will be set at 300 mg/dl to alert the nursing staff and providers of the risk of clinically significant hyperglycemic complication. If this occurs, the nursing staff will meet patient in the room to assess clinical status and will perform a POC glucose testing to confirm glucose values. If BG > 300 mg/dl, nursing staff will communicate this high glucose value to the primary care team. The primary care team will review patient record and insulin administration prior to determining need for additional corrective rapid-acting insulin. If patient has received corrective insulin within the past 2 hours, additional correction will not be given, and the blood

sugar will be re-checked in 1 hour. If the glucose value continues to rise with a rise indicated by CGM trend arrow, then additional corrective insulin will be given at that time.

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

Insertion of the CGM sensor will be performed per manufacturer instructions, and following an aseptic technique. After insertion of the sensors, providers will ensure proper hemostasis is achieved. Sensors will be removed if prolonged bleeding or severe pain occurs.

## 16. Potential Benefits to Participants

Subject participating in the standard group will not receive any direct benefits during the LTC stay, since treatment decision will be made based on POC BG (standard of care). Patients in the intervention group of CGM-GTS will also have a POC in the morning, but will benefit of 24/7 glucose monitoring to assess glycemic control. In addition, CGM with alarm may reduce the risk of hypoglycemia.

## 17. Compensation to Participants

Participants will receive one hundred dollars ($100.00) during the LTC stay. Total compensation will be one hundred dollars ($100). Compensation will be provided via ClinCard.

## 18. Data Management and Confidentiality

In order to assure each subject's confidentiality, data collected under this protocol will be coded and stored in a secure locked file cabinet with access limited to those directly related to the conduct of this study. Electronic versions of these data will be stored on a limited access, password protected, secure server with coded patient identifiers. Study participants will be assigned a code number that will be linked to their name. Only study personal will have access to the linked name-code key.

Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Principal investigator and other study personnel will not use data or PHI for any purpose other than conduction of the study. All PHI used will be de-identified and coded by the Principal investigator or designee. The code will be kept in a password protected computer file. PHI will be disclosed when required for audit by regulatory agency.

Information from medical records and from the procedures, interviews and tests that are part of this research will be collected. The personal information will be kept private and confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. The results of this study may be shown at meetings or published in journals to inform

other doctors and health professionals. Subject identity will be kept private in any publication or presentation about the study. People and organizations that may inspect and/or copy research records to assure the quality of the data and to analyze the data include:

- Medical staff who are directly or indirectly involved in patients' care related to this research;
- People who oversee or evaluate research and care activities at Emory University
- People from agencies and organizations that perform independent accreditation and oversight of research;
    - Emory offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research
    - Government agencies that regulate the research
    - Public health agencies
    - Research monitors and reviewer
    - Accreditation agencies

Data management and statistical analysis:

The present aims of this RCT is to investigate whether the Dexcom G6 CGM with Glucose Telemetry System (CGM-GTS) with hypoglycemia alarm may reduce the risk of hypoglycemia < 70 mg/dl (safety outcome) and improve glycemic control as measured by the percent of time in range (TIR) 70-180 mg/dl (efficacy end-point) in patients with T2D in subacute and long-term skilled nursing care facilities. Patients in the standard of care group will wear a blinded CGM and receive POC testing before meals and bedtime, with providers adjusting oral agents or insulin dose based on POC results. Patients in the intervention CGM group will have a single daily fasting POC testing and will wear a real-time Dexcom G6 with GTS, and providers will adjust oral or insulin therapy based on CGM-GTS profile information. Professor Limin Peng, PhD at the School of Public Health at Emory University will conduct statistical analyses.

For the safety endpoint, we will first compare the proportions of patients who have at least one episode of hypoglycemia by POC and by CGM. We will first perform nonparametric comparisons of the rate of hypoglycemia based on a two-sided Chi-square test (or Fisher's exact test in the presence of low incidence rates), followed by the Cochran-Mantel-Haenszel test, which adjusts for the potential center effect. Then we will perform univariate Poisson regression (or Negative Binomial regression) to assess whether there is any difference in the number of clinically significant hypoglycemia events between the two treatment groups. We will further conduct multivariate Logistic regression, Poisson regression (or Negative Binomial regression) to estimate the difference in the rate and frequency of hypoglycemia while adjusting for potential confounders. A glucose value < 70 mg/dl is considered as hypoglycemia requiring a nurse-driven response; thus, a BG <70 mg/dl will be used for sample size calculation. Data from Singh et al[75] a reduction of hypoglycemia was reported comparing the CGM/GTS system than POC (Sign et al 2020) per patient (0.67 episodes per patient, 95% CI 0.34-1.30

versus 1.69 episodes per patient, 95% CI 1.11-2.58, *p*= 0.024) [28]. Based on the results of the recent glargine U100 vs U300 study using CGM monitoring in the hospital, 56% had CGM BG readings <70 mg/dl (vs 14% with POC testing-standard of care), it is reasonable to assume 60% of resident on LTC facilities will experience one or more BG < 70 mg/dl by CGM. If we assume that 35% in the standard of care group will have at least one BG <70 mg/dl (based on linagliptin LTC study) [76], using one-sided, two-sample t-tests, we require we will need 70 patients per group to achieve 80% power.

| Hypoglycemia incidence, Rate in the CGM intervention group | 30% | 35% | 40% | 45% | 50% |
|---|---|---|---|---|---|
| Estimated sample size (N/group) for 80% power | 49 | 70 | 107 | 186 | 407 |

For the efficacy endpoint, we will compare mean daily glucose levels measured by CGM or POC, and percent TIR measured by CGM between treatment groups by nonparametric Wilcoxon-tests or two-sample t-tests, and by multivariate linear regression, which adjusts for other potential confounders such as age, gender, BMI, center, and admission HbA1c. A logarithm transformation may be employed to make the data better conform to the normality assumption. When conducting multivariate regression analyses, we will apply standard variable selection and model checking procedures to decide the final model. Stepwise, backward, or forward model selection strategy will be adopted to determine the variables to be included in the final model. Standard diagnostic and model checking procedures, such as deviance residual plot and Hosmer- Lemeshow test, will be applied to examine the fit of the developed models. To show non-inferiority between POC and CGM in terms of glycemic control, we set the equivalence margin of 18 mg/dl (1 mosm/l), from a view that a difference <18 mg/dl is usually not considered as clinically significant [60,61,77]. Based on the results from our recent CGM trials [28,78], it is reasonable to assume the standard deviation of mean daily BG is bounded above by 45 mg/dl. Assuming the true BG difference between the treatment groups is zero, and using one-sided, two-sample t-tests, we require 70 subjects for each treatment group to achieve 80% power.

## 19. Provisions to Monitor the Data to Ensure the Safety of Participants

Baseline and daily information will be entered by the study coordinators into data collection paper forms and into an electronic database (REDCap) provided by the Emory Research Information Technology Department. Baseline data will include demographics/history form (subject gender, age, ethnicity, type of treatment and comorbid conditions, body weight, BMI, laboratory results). Daily information will be collected on treatment, nutrition, blood glucose and laboratory values, complications and adverse events (hypoglycemia). The safety of interventions and treatments associated with this protocol will be under continuous review by

the investigative team. All adverse events will be reviewed bi-weekly in a multidisciplinary format that will involve review by a physician, and other members of the research team. All Serious Adverse Events will be reviewed within the applicable guidelines and submitted to the IRB and other appropriate regulatory bodies governing this study.
In addition, we have implemented protection against risks approaches as above to minimize the risk to our subjects.

**Stopping Rules:** We plan to perform interim analysis on the primary endpoint every 6 months and/or when half of the subjects have been randomized. The trial will be stopped if there is evidence beyond a reasonable doubt of a difference in the rate of death and hospital complications (two-sided alpha level, <0.01) between the treatment groups.
Plans for transmission of temporary or permanent suspension actions:
Any actions that mandate temporary or permanent suspension of study will be transmitted to the Emory IRB, and, if appropriate, to the FDA.

The frequency of protocol review will be: every 6 months.

The PI will forward reports of safety reviews within 15 days of the meeting to the Emory IRB.

See full Data safety monitoring plan in the attachment labeled Data Safety Monitoring Plan
A Data Safety Monitoring Board or Safety Officer has been designated for this study.

David Reyes, MD
Department of Medicine/Endocrinology

David C. Ziemer, MD, MPH
Department of Medicine/Endocrinology

## 20. Provisions to Protect the Privacy Interests of Participants

All participant data will be kept confidential and de-identified. Access to research will be limited to clinical investigators, research coordinators, and the IRB at Emory University. Clinical data will be stored in a secure web-based database that requires password access.

## 21. Economic Burden to Participants

There will be not economic burden on participants.

## 22. Consent Process

After identification of eligible patients, these individuals will be provided basic information regarding the study and, if interested, they will then be screened by research staff using the inclusion/exclusion criteria delineated elsewhere in this protocol. Research staff will approach participants by phone to find out their possible interest in the study. If participants agree, the research staff will meet with them in their room to explain the study procedures in person. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have any questions, and research staff will answer these questions. The principal investigator will also be available to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed in accordance with the IRB guidelines of Emory University. Residents will be informed that participation in the study is voluntary and there are other forms of treatment available to control their blood glucose levels. They will be given time to ask any questions they have about the study. They will also be informed that their care will not be affected if they choose not to participate. Consent process will take place in residents' room. In the event where primary care team deems that the resident not able to give informed consent, research coordinator will approach their LAR by phone.

A copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office. A copy of the consent will be sent via email or by mail when the LAR has provided verbal consent or requests a full copy prior to providing consent for their relative.

Adults who speak any of the following languages (English, Russian, Spanish and Arabic) will be approached for participation in the study.

**Cognitively Impaired Adults and Adults Unable to Consent**

Long-term care residents with diabetes have higher rates of serious comorbidities and have greater activity of daily living dependencies than residents without diabetes. The present study aims to determine if CGM -GTS will benefit the management and reduce the risk of hypoglycemia in long-term care residents with T2DM. Research staff will ask the primary care team about the resident's cognitive status and ask if they are able to consent. If the primary team deems the patient is not able to give informed consent then we will approach the legal representative (durable power of attorney for health care, court appointed guardian for health care decisions, spouse, or adult child). During the progress of the study the primary team will be monitoring the cognitive status of the participant. In the instance that the patient has a legal representative, the study procedures will be described to them. The resident's legal representative will be approached by phone to inform the study activities, benefits, and risks. They will be given time to ask any questions they have about the study and the opportunity to discuss with the potential enrollee as well. The legal guardian will be informed that the study is voluntary and that care of their relative will not be affected if they choose not to participate.

## 23. Setting

Identification and recruitment of patients will occur in Grady (Crestview Health and Rehabilitation Center) and Emory affiliated subacute rehab and skilled nursing facilities which include: Budd Terrace Nursing Home and A.G. Rhodes Wesley Woods.

## 24. Resources Available

Potential subjects will be identified by their treating physicians and referred to the researchers. Residents' private and identifiable information will not be shared prior to receiving permission from the resident to do so. All residents with history of diabetes will be considered for participation. The research team and/or the research coordinators will also review resident's medical records and laboratory tests to identify potential candidates. Once identified, the investigators and/or research coordinators will discuss the protocol with the attending physician taking care of the resident and request permission to include him/her in the trial. If the primary physician agrees to include the resident in the trial, then the resident will be invited to participate in the study. Potential candidates will be informed that there are other forms for glucose monitoring available to manage their diabetes. Long-term care residents will be instructed both verbally and in the written informed consent form that their participation in the study is entirely voluntary and that they can withdraw at any time, which will in no way compromise or alter the usual care that they would otherwise receive. They will also be given the phone numbers of the PI, IRB chair and Grady official to whom they can address any questions or concerns.

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