DEMONSTRATION OF AN ARTIFICIAL INTELLIGENCE BASED CLOSED LOOP GLUCOSE CONTROL SYSTEM AS A THERAPEUTIC MODALITY IN TYPE 1 AND TYPE 2 DIABETIC PATIENTS

NCT Number: 05644730

Principal Investigator: Dr. Francisco Pasquel

August 22, 2022

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Protocol Number: IMT 2022-1

National Clinical Trial Identified Number: NA

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Sponsor: Ideal Medical Technologies

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Funded by: Ideal Medical Technologies

Version Number: 1.0.7

22 August 2022

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Explanation of glucose control software (Page 19)	1. Removed reference to fuzzy logic. 2. Added improved explanation around fact that the FUSION devices glucose control software is an expert based rule system, or knowledge based system.	1. The FUSION system does not use fuzzy logic. 2. To better describe the basis for how the FUSION systems glucose control software works.
Termination Criteria (Pages 62-64)	1. Removed redundant termination criteria section (8.1.1.7). 2. Addition of DKA, Severe Hyperglycemia and HHS. 3. Addition of excessive volume administration with defined fluid limit to stop study. 4. Addition of any unanticipated adverse device effect (UADE). 5. Removed confusing term “halting criteria”.	1. To protect subjects if device cannot prevent development of DKA, Severe Hyperglycemia, or HHS. 2. To protect subjects from excessive volume loading. 3. To protect subjects from harmful device effects. 4. To use consistent terminology to describe a permanent stopping of the study.

	6. Defined criteria for stopping study on one subject, and for entire study.	5. To clarify stopping criteria for study personnel.
Discharge criteria (Pages 103-104)	1. Defined criteria that need to be met before subject may be discharged from the CRC, including glucose measurement criteria and length of time they need to be observed after the end of the closed loop glucose control session.	1. To better describe for the study nurse the criteria that need to be met prior to discharge.
Frequency of Reference Glucose Values (Pages 103-104)	1. Clarified how often Reference Glucose Values will be obtained under different circumstances.	1. To clarify for study personnel the circumstances under which Reference Glucose Values will be checked every 10, 30 or 60 minutes.
Diabetic Ketoacidosis screening (Page 54)	1. Added criteria to screen for diabetic ketoacidosis if the Reference or Dexcom G6 CGM(s) have been greater than 200 mg/dL for more than one hour consecutively.	1. To screen for diabetic ketoacidosis if the subject is experiencing persistent hyperglycemia.
Screening prior to initiation closed loop glucose control session (Time 0 to 5 hours, page 54).	1. Added screening criteria to make sure subjects are not in DKA before entering the study, and to also make sure they are not acutely ill with any other illness, prior to starting the study.	1. To prevent using the FUSION system on an acutely ill or unstable subject.
Use of device – Electrostatic Discharge (Protocol 2, page 97)	1. Added instructions to mitigate against risk of introducing an electrostatic discharge to the FUSION system.	1. To prevent an electrostatic discharge from adversely affecting the performance of the FUSION system.
Length of use of medication syringes (time 5 to 29 hours, page 59)	1. Added instructions to not use the medication syringes for a period of time exceeding 24 hours.	1. To avoid using the medication syringes for a period of time exceeding 24 hours, as the biocompatibility of the medications in the syringes is unclear for a period of time exceeding 24 hours and is thus not FDA approved.

Necessary equipment (time 0 to 2 hours, Pages 53-54)	**1. Specified equipment to be on hand in the CRC, including cardiac monitor, pulse oximeter, blood pressure cuff, and resuscitation cart.**	**1. To make sure CRC has adequate equipment on hand to both monitor and resuscitate the subject.**
Synopsis (page 4)	**1. Increased study size from two type 2 diabetic subjects to two type 1 diabetic subjects and six type 2 diabetic subjects.**	**1. To update the study size.**
Labs (page 6)	**1. Added hemoglobin to screening labs**	**1. To exclude subjects who do not have normal hemoglobin levels, given that the study subjects may have up to 80 mL of blood drawn during the course of the study.**
Rescue Medicine (Pages 38 & 62)	**1. Added Glucagon**	**1. To give additional option for treatment of hypoglycemia.**
Meal Plan (Page 58)	**1. Changed closed loop control session start time to 1200 with first meal being lunch**	**1. To allow CGM's time to warm up and verify their accuracy, prior to starting the study**
Entire Document	**1. Changed length of study to 32 hours 2. Changed interval for checking Reference Glucose Values to every 10-60 minutes 3. Changed document version year to 2022 to reflect year submitted to IRB, and version number to 1.0.7**	**1. To ensure consistency within the document 2. To ensure consistency within the document, and to cover all possible intervals between Reference Glucose Values 3. To update document to coincide with year of submission to IRB and most recent version number**
Protocol 1 (Page 95)	**1. Changed carrier solution for FUSION systems insulin and dextrose infusions from normal saline to ½ normal saline**	**1. To reflect agreement with FDA to use a hypo-osmotic carrier solution to minimize risk of vein irritation from infusion of hyper-osmolar D10 normal saline solution used by the FUSION system**

Study Data Identification **(Pages 79)**	**1. Clarified that only de-identified data will be used in the study**	**1. To ensure protection of the study subjects and any study subject data obtained through the subject's participation in the study**
Role of IMT Personnel **(Pages 85)**	**1. Clarified role IMT personnel will have in the study – limited to use of the FUSION system with no study subject interaction, no provision of study subject medical care, and no extraction or analysis of the study data**	**1. To prevent IMT personnel from becoming involved in study subject medical care and to protect the integrity of the studies data for purposes of future regulatory submissions**
Method of use of the Dexcom G6 CGM system by the FUSION system **(Page 39)**	**1. Stated that the FUSION system uses a simple average of the two Dexcom G6 CGM systems to effect glucose control.** **2. Clarified that the FUSION system will continue to operate for up to 4 hours on the glucose data from only one Dexcom G6 CGM.** **3. Clarified that the FUSION system will continue to operate for up to 20 minutes if no glucose data is available from either Dexcom G6 CGM system.**	**1. To clarify for study personnel how the FUSION system uses the data from the two Dexcom G6 CGM systems.**
Method of communication between the Dexcom G6 CGM transmitter and receiver **(Page 40)**	**1. Stated that the Dexcom G6 CGM Sensor/Transmitter pair communicate with the Dexcom G6 CGM Receiver via Bluetooth.** **2. Stated that the method of communication of the Dexcom G6 CGM system has not been altered in any way by IMT personnel.**	**1. To clarify for the study personnel that IMT has not altered, in any way, how the Dexcom G6 CGM system functions.**
Method and accuracy of data extraction of glucose values from the Dexcom G6 CGM Receiver by the FUSION system	**1. Stated that the FUSION system uses a software Driver to extract the glucose values from the Dexcom G6 CGM Receiver.** **2. Also noted that the FUSION system is connected to the Dexcom G6 CGM Receiver by a serial data cable.**	**1. To clarify for study personnel how the FUSION system extracts glucose data from the Dexcom G6 CGM Receiver.** **2. To clarify for study personnel that the Dexcom G6 Receiver transfers its data to the computer running the FUSION**

(Page 40)		**systems software via a data cable.**
Reference Glucose Values **(Pages 37-38)**	**1. Stated that results from the Nova StatStrip Hospital Glucose Meter System glucose meter will be used as Reference Glucose Values** **2. Stated that if the retrograde hand vein is no longer available for blood draws for Reference Glucose Values, that capillary blood from a fingerstick could be used as a Reference Glucose Value.**	**1. To clarify that only the Nova StatStrip Hospital Glucose Meter System will be used to analyze whole blood samples Reference Glucose Values.** **2. To increase the likelihood of finishing the study if the retrograde hand stops functioning.**
Human subject data **(Pages 29-30)**	**1. Listed demographic and glucose metric results from the first two subjects treated with the FUSION system, as well as glucose versus time graphs with overlayed infusion data.**	**1. To note the performance characteristics of the FUSION system in its first in human study.**
Risk assessment – compression artifact **(Pages 30, 41, and 106)**	**1. Noted risk of a false low glucose value from compression of the local Dexcom G6 sensor site due to subject laying on this site.** **2. Documented accuracy of posterior upper arm site for Dexcom CGM in clinical study, to inform FDA of the validity of using this alternative site.** **3. Clarified that the two Dexcom CGM's should be placed on contralateral sides if a replacement CGM is placed in the posterior upper arm position(e.g., right abdomen and left arm)**	**1. To document this additional risk and clarify for the study nurse steps needed to mitigate this risk.** **2. To inform FDA that the posterior upper arm site is a valid site for CGM placement.** **3. To decrease risk of subject compressing both CGM's at the same time.**
Risk assessment – Volume overload **(Pages 41-42)**	**1. Documented the tendency of the FUSION system to deliver approximately 25% of the subject's total daily fluid needs.**	**1. To reinforce for study personnel the importance of selecting out subjects with renal or cardiac disease who are more likely to suffer side effects from volume overload.** **2. To clarify for study personnel the need to monitor the**

		subjects for signs of excessive volume overloading
Recovery Period **(Pages 107-109)**	**1. Defined the subcutaneous insulin dosing provided after the conclusion of the closed loop glucose control session.**	**1. To clarify for study personnel the method for transitioning the subjects from the closed loop glucose control session to glucose control via subcutaneous insulin injections or CII via an insulin pump.**
Reference Glucose Value **(Throughout the document)**	**1. Defined the term "Reference Glucose Value" and used consistently throughout the document.**	**1. To clarify for study staff the difference between a Reference Glucose Value and a CGM glucose value.**
CGM Placement **(Pages 104-105)**	**1. Noted proper position for CGM placement, including alternative placement site.**	**1. To clarify for study staff the proper abdominal position for CGM placement, and to alert them of the availability of using the posterior upper arm position as an alternative placement site.**
Instructions for Subject Prior to Visit 3 **(Page 53)**	**1. Clarified the timing to withhold oral anti-hyperglycemic medications prior to visit 3.**	**1. To clarify for study staff and the subjects when they should begin to withhold their oral anti-hyperglycemic medications prior to visit 3.**
Hypoglycemia Treatment **(Page 62)**	**1. Clarified when to treat hypoglycemia and its related symptoms.** **2. Clarified the treatment methods available for hypoglycemia.** **3. Defined and documented the need to treat neuroglycopenia.**	**1. To clarify and educate the study staff when and how to treat hypoglycemia.**
Halting versus Termination Criteria	**1. Removed the term "Halting Criteria" from the document.** **2. Clarified the different criteria for terminating the study on one subject versus terminating the entire study.**	**1. To consistently use one term (e.g., "Termination Criteria") to signify the permanent end of the study on either one subject or the entire study.**

(Throughout document)	**3. Added excessive blood removal during visit 3 as a termination criterion (Page 102).** **4. Added excessive volume administration from FUSION system.**	**2. To clarify for study staff the different criteria for terminating the study on one subject versus terminating the entire study.**
Criteria to Replace CGM's **(Pages 105-106)**	**1. Clarified criteria whereby the CGM(s) should be replaced.**	**1. To clarify this issue for study staff.**
CGM Validation Criteria **(Page 105)**	**1. Clarified criteria whereby the CGM should be calibrated.** **2. Clarified that either one or both CGM's may need calibration at the same time.** **3. Clarified that it is possible to go the entire study without calibrating the CGM's.**	**1. To clarify this issue for study staff.**
Noted new FUSION system alarm features **(Page 106)**	**1. To document the Compression Artifact and CGM Discrepancy (e.g., CGM's > 20% different than their averaged value) alarms added to the FUSION system**	**1. To alert study staff to these new features of the FUSION system**
Added C-Peptide to study labs **(Page 6)**	**1. To test for lack of endogenous insulin production in type 2 diabetic subjects.**	**1. To avoid inadvertent classification of type 1 diabetic subjects as type 2 diabetic subjects.**
Risk Assessment **(Pages 41, 44-45)**	**1. Added Volume Overload, Severe Hyperglycemia, DKA, and HHS to risk assessment section.**	**1. To clarify for study staff that these are risks of this study, including during the closed loop glucose control session.**
Updated Exclusion Criteria **(Page 50)**	**1. Added any form of renal failure or congestive heart failure to exclusion criteria.** **2. Added low C-Peptide levels as an exclusion criteria for type 2 diabetic subjects.**	**1. To prevent exacerbation of an underlying chronic health condition due to excessive fluid loading from the FUSION system.** **2. To prevent use of the FUSION system on more than two type 1 diabetic subjects.**

Updated Care provided in visit 3 **(Page 100)**	**1. Clarified the insulin dosing given to subjects in the 5 hour period prior to starting the closed loop session on visit 3.** **2. Clarified that the study nurse will give all insulin injections in the CRC.** **3. Clarified that the insulin given to subjects in the CRC will be provided by the CRC (e.g., subject may not use their own insulin).**	**1. To clarify these issues for study staff and the subjects.** **2. To increase control over the care provided to the subjects during visit 3.**
Pre-Study assessment at beginning of visit 3 **(Page 54)**	**1. Clarified the labs to be performed on the subjects prior to proceeding with the closed loop session on visit 3.** **2. Documented which Ketone meter will be used during the above assessment.**	**1. To clarify this issue for study staff.**

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) and the following:

- Applicable standards as set forth by the NIH and/or FDA.

National Institute of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

DEMONSTRATION OF AN ARTIFICIAL INTELLIGENCE BASED CLOSED LOOP GLUCOSE CONTROL SYSTEM AS A THERAPEUTIC MODALITY IN TYPE 1 AND TYPE 2 DIABETIC PATIENTS

Study Description:

Tight glucose control in the Intensive Care Unit (ICU) setting is difficult to achieve. We hypothesize that a closed loop glucose control system based on artificial intelligence (AI) will improve upon the glucose control currently achieved by open loop systems, and may improve the outcomes of critically ill patients, including those with COVID-19. This Earl Feasibility Study (EFS) will test the ability of a prototype artificial intelligence based closed loop glucose control system named FUSION, to provide safe and effective glucose control in subjects with type 1 and type 2 diabetes in a clinical research center (CRC) setting. Subjects with type 1 diabetes have been chosen as they lack native Insulin production, which makes it

challenging to provide safe and effective glucose control for them. Subjects with type 2 diabetes have been chosen as they are insulin resistant, which makes their insulin resistance profiles like that of ICU patients. As this is a continuation of a first in human study of a new medical device, the controlled environment of the CRC is preferable to the less controlled environment of an ICU setting.

Objectives:

Primary Objectives:

1. The primary safety objective of this first in human study is to test the hypothesis that an AI based closed loop glucose control system will be able to safely control the blood glucose levels of participants with type 1 and type 2 diabetes during a 24 hour stay in the CRC setting.
2. The primary efficacy objective of this first in human study is to test the hypothesis that an AI based closed loop glucose control system will effectively control the blood glucose levels of participants with type 1 and type 2 diabetes during a 24 hour stay in the CRC setting.

Secondary Objectives:

The secondary objectives of this study are to test the hypothesis that an AI based glucose controller will be effective in minimizing glucose curve variations commonly observed in critically ill patients.

Endpoints:

Primary Endpoint:

1. The primary safety endpoint will be the percent of all glucose values that are within the glucose range of less than < 70 mg/dL. Time frame will be from start of use of AI controller until end of use of AI controller.
2. The primary efficacy endpoint will be the percent of all glucose values that are within the glucose range of 70-180 mg/dL.

Time frame will be from start of use of AI controller until end of use of AI controller.

Secondary Endpoints:

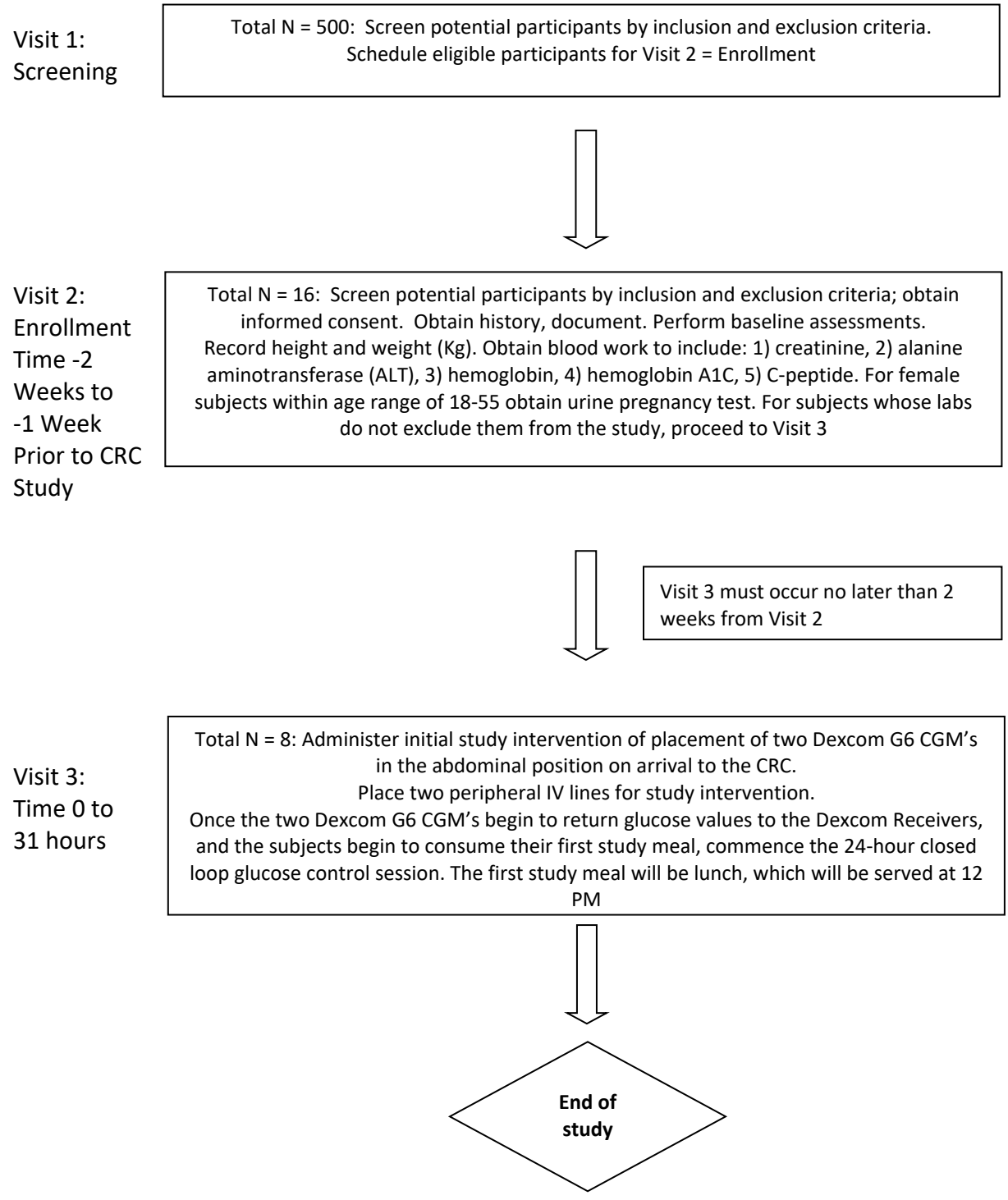
- Measure the percent of glucose values that are within clinically significant hypoglycemic range (glucose <54 mg/dL).
- Measure the percent of glucose values that are within the moderate hypoglycemic range of 54-69 mg/dL.
- Number of hypoglycemic events as measured by glucose < 70 mg/dL.
- Measure the percent of glucose values that are within the desired glucose control range of 100-140 mg/dL.
- Measure the percent of glucose values that are within the range of 70-140 mg/dL.
- Measure the percent of glucose values that are within the hyperglycemic range of >140 mg/dL.
- Measure the percent of glucose values that are within the range of 70-180 mg/dL.
- Measure the percent of glucose values that are within the hyperglycemic range of >180 mg/dL.
- Mean glucose level.
- Measure of dispersion – coefficient of variation (CV).
- The study data will be used to determine the percentage of paired glucose values (continuous glucose monitor(s) and Reference Glucose Value) in each zone using a Clarke error grid analysis.[1] These calculations will be performed for each individual CGM system and for the glucose value used by the FUSION system for purposes of glucose control (a calculated average of the two CGM systems).

Time frame will be from start of the use of AI controller until end of use of AI controller.

Study Population: Two participants with type 1 diabetes and six participants with type 2 diabetes, male and non-pregnant females, ages 18-70 inclusive, admitted to a CRC. Participants will eat three standardized meals during their 24-hour closed loop glucose control study.

Phase:	Early Feasibility Study, First in Human.
Description of Sites/Facilities Enrolling Participants:	Emory University Hospital, a tertiary care facility located in Atlanta, Georgia, United States. Single center study, all enrollments within USA.
Description of Study Intervention:	The medical device to be tested is named FUSION and is a fully functional closed loop glucose control system (artificial pancreas). The system consists of three main components: **1)** Two Dexcom G6 continuous glucose monitors (CGM) provide glucose values to the glucose control software, **2)** Glucose control software that is run by an all in one Medical Computer that is mounted on a powered Medical Cart, and which uses an artificial intelligence technique to determine, in an iterative fashion, the infusion rates of intravenous (IV) insulin and/or dextrose into the type 2 diabetic subjects for purposes of controlling their blood glucose into the range of 100-140 mg/dL, **3)** Two syringe pumps that are used to infuse insulin and/or dextrose into the study subjects. These syringe pumps are connected by serial data cables to the Medical Computer that runs the glucose control software, and their infusion rates are controlled by the glucose control software. Reference Glucose Values are measured every 10-60 minutes on the Nova StatStrip Hospital Glucose Meter System point of care glucose meter to ensure subject safety.
Study Duration:	Six months.
Participant Duration:	Thirty-two hours.

1.2 SCHEMA


Visit 1: Screening
Total N = 500: Screen potential participants by inclusion and exclusion criteria. Schedule eligible participants for Visit 2 = Enrollment
Visit 2: Enrollment Time -2 Weeks to -1 Week Prior to CRC Study
Total N = 16: Screen potential participants by inclusion and exclusion criteria; obtain informed consent. Obtain history, document. Perform baseline assessments. Record height and weight (Kg). Obtain blood work to include: 1) creatinine, 2) alanine aminotransferase (ALT), 3) hemoglobin, 4) hemoglobin A1C, 5) C-peptide. For female subjects within age range of 18-55 obtain urine pregnancy test. For subjects whose labs do not exclude them from the study, proceed to Visit 3
Visit 3 must occur no later than 2 weeks from Visit 2
Visit 3: Time 0 to 31 hours
Total N = 8: Administer initial study intervention of placement of two Dexcom G6 CGM's in the abdominal position on arrival to the CRC.
Place two peripheral IV lines for study intervention.
Once the two Dexcom G6 CGM's begin to return glucose values to the Dexcom Receivers, and the subjects begin to consume their first study meal, commence the 24-hour closed loop glucose control session. The first study meal will be lunch, which will be served at 12 PM
End of study

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Visit 1: Screening	Visit 2: Enrollment Time -2 weeks to – 1 week	Visit 3: Perform Baseline assessments Place Dexcom CGM monitors Time 0 to 5 hours	Visit 3: Perform closed loop glucose control session Time 5 to 29 hours	Visit 3: Observe subject for two hours after completion of the closed loop glucose control session Time 29 to 32 hours
Informed consent		X			
Demographics	X	X			
Medical history	X	X	X		
Administer study intervention			X	X	X
Concomitant medication review		X	X		
Physical exam		X	X		
Vital signs			X	X	X
Height			X		
Weight	X	X	X		
Hemoglobin and Hemoglobin A1C		X			
Sserum ALT & creatinine		X			
C-Peptide (subjects with type 2 diabetes)		X			
Pregnancy test [a]		X			
Adverse event (AE) review and evaluation			X	X	X
Complete Case Report Forms (CRFs)		X	X	X	X

a Urine pregnancy test (women of childbearing potential).

2 INTRODUCTION

2.1 STUDY RATIONALE- GLYCEMIC CONTROL IN THE ICU

In the U.S. there are currently 80,000 adult ICU beds, and 6 million admissions per year of ICU patients into these beds.[2] The cost to care for these ICU patients is approximately 150 billion dollars per year.[3] At least 75% of ICU patients suffer from dysglycemia – hypoglycemia, hyperglycemia and increased glucose variability.[4] The hyperglycemia is the result of a relative insulin resistance that is caused by the elevation of the stress hormones glucagon, cortisol, growth hormone, epinephrine and norepinephrine in these critically ill patients.[5] The hypoglycemia and increased glucose variability occur because of the ineffectiveness of the current methods of controlling blood glucose levels in these patients.

Poor control as reflected by high rates of hypoglycemia, hyperglycemia, and increased glucose variability have been associated with increased morbidity and mortality rates in ICU patients. This deleterious effect is caused by impaired function of the infection fighting white blood cells, and by augmentation of the bodies' inflammatory cascades, both of which can impair organ function including the kidneys, bone marrow, lungs and heart.[5] A large prospective randomized study published in 2001 showed that tight glucose control in Intensive Care Unit (ICU) patients decreased their morbidity and mortality rates by 30-40%.[6] Over the past 20 years multiple studies have confirmed the benefits of effective glucose control in the ICU setting, with these benefits extending to all patients in the ICU, not just those with diabetes.[7-10] It should be noted these benefits have been seen in medical,[11] cardiac,[12] and trauma[13] ICU settings.

As noted below (Figure 1) mortality rate increases as the degree of hypoglycemia increases. In this study of 4,946 ICU patients, the control patients had no glucose values less than 81 mg/dL, and as a result had an overall mortality rate that was 46% lower than the group of patients who suffered at least one hypoglycemic event.[14]

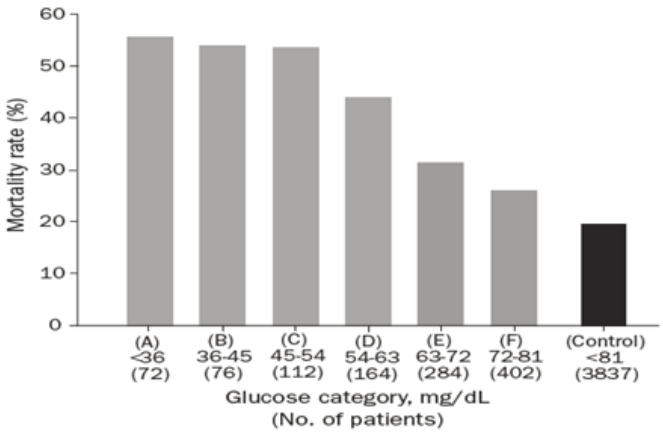


Figure 1 - Hypoglycemia zones (A, B, C, D, E, F) reflect lowest glucose value recorded. Egi, Mayo Clinic Proceedings, 2010

Shown below (Figure 2) are the deleterious effects of both higher average glucose values and increasing glucose variability (CV = coefficient of variation) in a study of 4,084 ICU patients.[15]

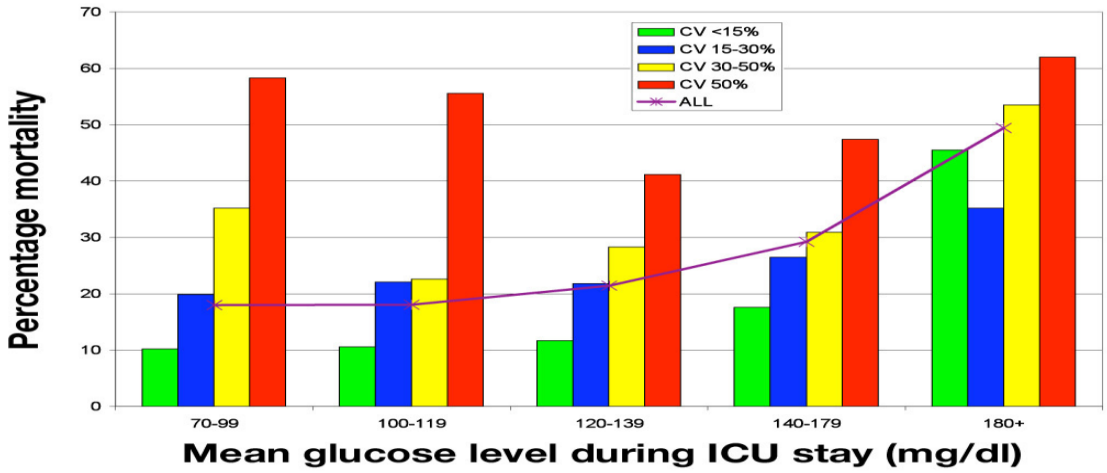


Figure 2 – Patients divided into quintiles based on their average ICU glucose levels. Each quintile further divided based on the patients CV. CV = Coefficient of Variation. Krinsley, Journal of Diabetes Science and Technology, 2009.

As can be deduced from Figure 2, the best patient outcomes would be achieved by maintaining a mean blood glucose level in the range of 70-139 mg/dL while at the same time keeping the variability, as measured by the coefficient of variation, to less than 15%.

It is also essential to maintain the ICU patient's glucose level in the clinician prescribed range. Seen below (Figure 1) are results from 2,550 non-diabetic ICU patients.[16] The prescribed range being used for this study was 70 – 140 mg/dL. For purposes of analysis, there were an equal number of patients in the high time in range (TIR hi) and low time in range (TIR lo) groups. The patients with a high time in range (TIR hi) had a median percent time in range of 94%, while those with a low time in range (TIR lo) had a median value of 61%. The overall mortality rate for the patients with a low time in range was 86% higher than the high time in range group. This study showed that mortality rates decrease significantly when the glucose time in range 70 – 140 mg/dL exceeds 90%. Non-diabetic ICU patients are more susceptible to the adverse effects of dysglycemia than are diabetic patients, and overall represent 75% of all ICU patients.

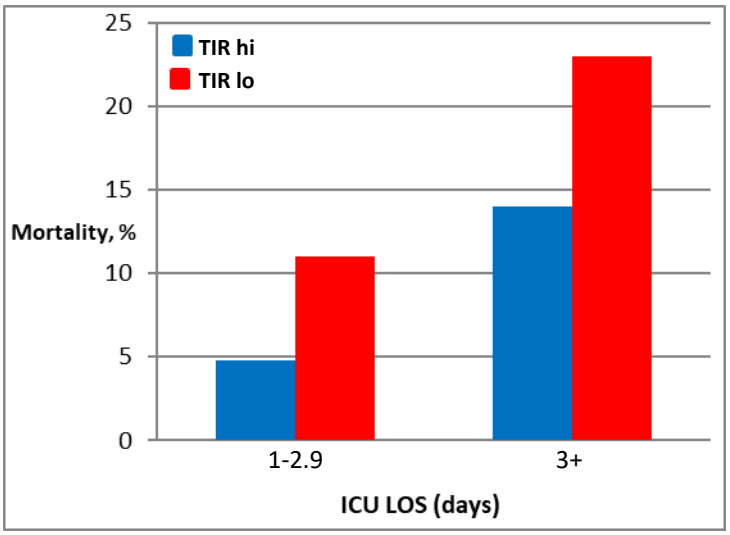


Figure 1*– Equal number of patients in the TIR hi and TIR lo groups. LOS = Length of stay. TIR = time in range. Krinsley, Critical Care, 2015.*

Despite the obvious benefits of tight glucose control that are seen in Figures 1-3, almost all studies to date have failed to achieve effective tight glucose control, especially when it is defined as time in range of 70- 140 mg/dL exceeding 90%, hypoglycemia (< 70 mg/dL) rate of less than 0.1%, and glucose variability as measured by a CV of less than 15%. This inability to effectively control blood glucose levels in critically ill patients has led to incorrect conclusions from some studies.

In a large randomized prospective tight glucose control study of 6104 patients known as the NICE-SUGAR study,[17] the tight glucose control group (range 81-108 mg/dL) actually had higher mortality rates than the control group (glucose < 180 mg/dL) – 27.5 vs 24.9% mortality rates. However, the tight glucose control group had a severe hypoglycemia (<= 40 mg/dL) rate of 6.8%, versus 0.5% in the control group. This large hypoglycemia rate in the tight glucose control group would have significantly increased the mortality rate of this group, as can be seen above (Figure 1). This confounding variable most likely led to the higher mortality rate in the tight glucose control group. In a post hoc analysis of their glucose data, the NICE-SUGAR investigators noted that there was an association between both moderate (41-70 mg/dL) and severe (<= 40 mg/dL) hypoglycemia and mortality rates in the patients they studied.[18] The patient group that did not suffer from any hypoglycemia had a mortality rate of 23.5%, versus 28.5% and 35.4% in the moderate and severe hypoglycemia groups ($p<0.001$ for both groups). The odds ratios of death were 1.6 and 2.6 in the moderate and severe hypoglycemia groups as compared to the patients who did not suffer any hypoglycemia. This confirms the importance of avoiding hypoglycemia while attempting to maintain tight glucose control in the ICU setting.

After it was originally determined that tight glucose control improves ICU patient outcomes, multiple methods aimed at achieving tight glucose control in this challenging patient population were developed. The original method was paper based intravenous insulin dosing protocols.[19] To utilize these, the nurse would manually measure the patient's blood glucose level, then refer to the institutions paper based protocol to determine if any adjustment in the current intravenous insulin dose was needed, then go to the intravenous pump to make an adjustment to the intravenous insulin infusion rate. This cycle would repeat itself every 1-4 hours, and is referred to as open loop control, as there continues to be human intervention in the control process.

The next step in improving glucose control was to utilize two standard engineering control methods. Glytec LLC, has created glucose control software based on a Proportional Derivative technique.[20] This glucose control software is sold to hospitals as Glucommander, and serves to replace home grown paper based protocols, although it is still an open loop method. The nurse still manually measures the patient's blood glucose level, enters the value into the Glucommander software, and then manually enters the new insulin dose recommended by the software into the bedside intravenous pump every 1-4 hours. Monarch Medical Technologies utilized a Model Predictive Control technique to create its EndoTool glucose control software.[21] This open loop system works similar to the Glucommander software.

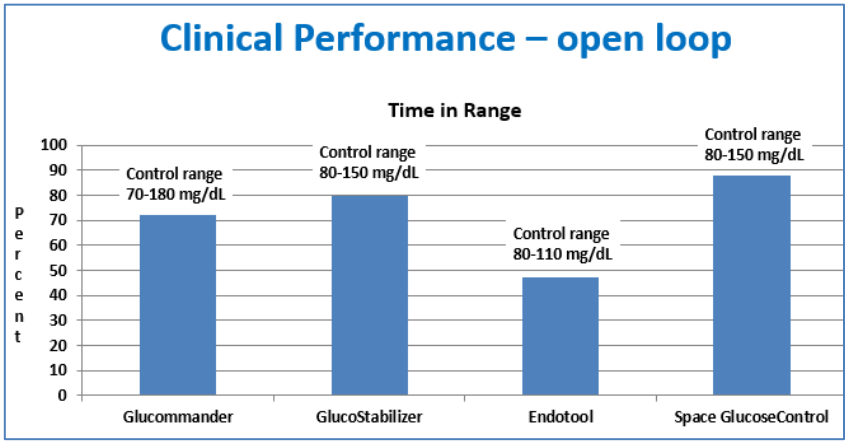


Figure 2– Although different ranges were reported, none were able to achieve > 90% time in range.

While the software-based insulin dosing calculators represent an improvement over paper-based protocols, they still are not capable of achieving a time in range (e.g., 100 – 140 mg/dL) that exceeds 90%, while at the same time avoiding any significant time in the hypoglycemic range and reducing glucose variability. In a poster presentation presented at the 2016 American Diabetes Association meeting, it was noted that when Glucommander was used in 340 adult ICU patients with sepsis, it produced a time in range (70 – 180 mg/dL) of 72%, and a hypoglycemia (< 70 mg/dL) rate of 0.51%.[22] In a study done on 2,398 medical/surgical ICU patients, Glucostabilizer achieved a time in range (80-150 mg/dL) of 80.4% and hypoglycemia (<70 mg/dL) rate of 3.5%. In a study done on burn patients, Endotool was noted to achieve a time in range (80 – 110 mg/dL) of 47% and a hypoglycemia (<80 mg/dL) rate of 4.5%.[23] In a multi-center medical ICU study on 508 patients, the Space GlucoseControl system time in range (80-150 mg/dL) was 83% and hypoglycemia (<80 mg/dL) rate was 2.3%. These results for time in desired control range and hypoglycemia are summarized here (Figure 2, Figure 3).

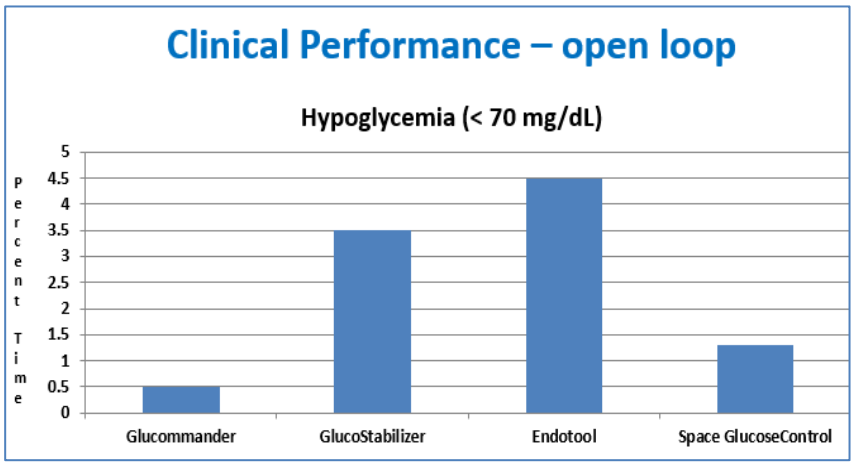


Figure 3– Patient types treated were: Sepsis (Glucommander), medical/surgical ICU (GlucoStabilizer), burn ICU (Endotool), medical ICU (Space GlucoseControl). Endotool and Space GlucoseControl hypoglycemia rates are for < 80 mg/dL.

It should be noted that the standard of care for achieving tight glucose control in ICU patients is insulin delivery via the intravenous route, and that ICU nurses will spend 90-120 minutes per patient per day attempting to achieve tight glucose control with the current methodologies.[24]

One of the reasons tight glucose control is so difficult to achieve is that the blood glucose versus time curve is highly nonlinear in nature. To achieve tight glucose control, a control system capable of handling a nonlinear state will need to be employed. Most prior attempts to achieve glucose control utilizing

control theory have employed Proportional, Integral, Derivative (PID) controllers.[25] These controllers were originally developed for linear systems,[26] thus they so far have enjoyed limited success in glucose control.[22] Newer computerized glucose management systems, such as Endotool,[27] utilize Model Predictive Control (MPC) theory[28] and have enjoyed improved success compared to PID controllers in keeping blood glucose in the desired range, and limiting the incidence of hypoglycemia. However, these systems still focus solely on the glucose lowering effects of insulin and do not consider the glucose elevating effects of glycogenolysis/gluconeogenesis – from the liver. This causes them to have unacceptably high rates of hypoglycemia and low time in the desired range,[29] thus they are not suitable in their current format for creating a closed loop glucose control system for use in the ICU setting. The failure of PID and MPC based glucose controllers to achieve safe and effective tight glucose control has led to the need to consider alternative control techniques.

2.2 STUDY RATIONALE – COVID-19

The current COVID-19 pandemic is caused by a Coronavirus that shares at least 80% of its RNA with the Coronavirus that caused the 2003 SARS epidemic. During the 2003 SARS epidemic it was shown that admission plasma glucose levels were an independent predictor of increased mortality rates (Figure 4).[30]

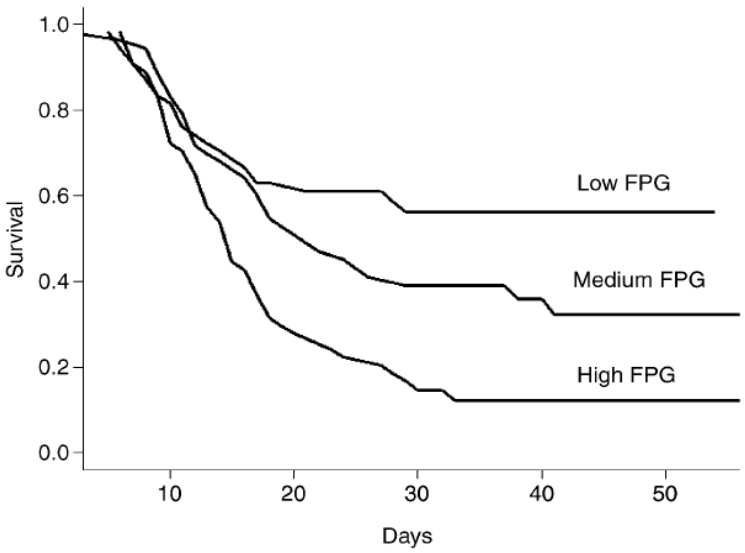


Figure 4 – Patients were divided into terciles based on admission fasting plasma glucose (FPG) levels. Survival is correlated with the admission fasting plasma glucose (FPG). Low FPG 3.3-5.78 mmol/l, Medium FPG 5.78-7.9 mmol/L, High FPG 7.9-29.1 mmol/L. Yang, Diabetic Medicine, 2005.

In a recently published article on over one-thousand U.S. COVID-19 patients, it was shown that the presence of either diabetes or uncontrolled hyperglycemia in non-diabetic patients increased mortality rates by more than 400% (Figure 5).[31] The glucose metrics, mortality rates, and length of stay data for the two groups in this study are seen below (Table 1).

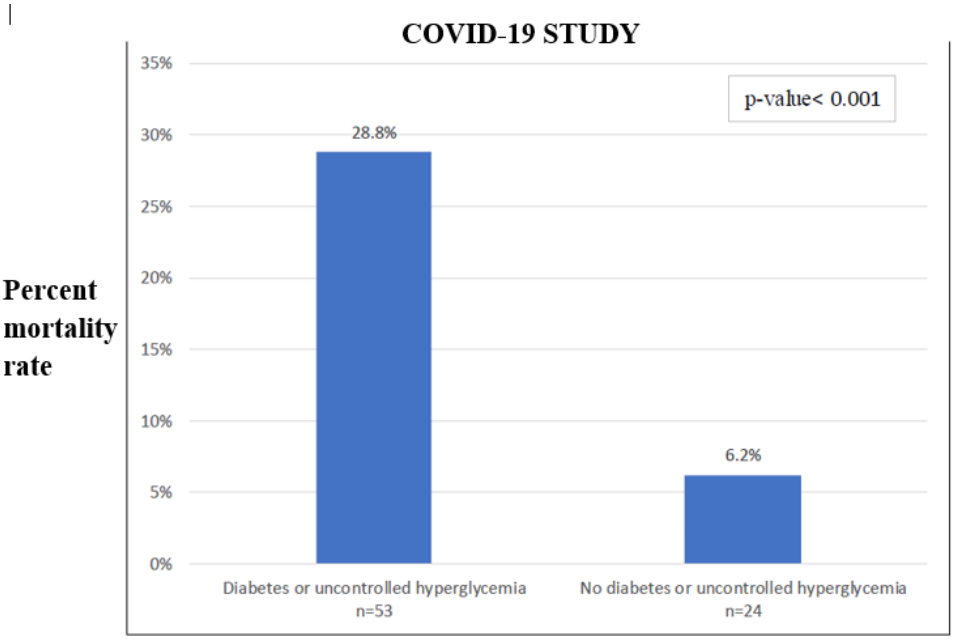


Figure 5- Mortality rates among patients with diabetes or uncontrolled hyperglycemia (n=184), versus patients without diabetes or hyperglycemia (n=386). Diabetes defined as HbA1c >= 6.5%. Uncontrolled hyperglycemia defined as two glucose values >180 mg/dL in a 24-hour period. The n=53 and n=24 represent the number of patients who died in each group. Bode, Journal of Diabetes Science and

	No DM/No UH (N=671)	DM/UH (N=451)	p
Mean admission glucose mg/dL	114.5 (±20)	202.4 (±118)	<0.001
Mean hospital glucose mg/dL	116.6 (±25.9)	178.5 (±71)	<0.001
% time in range > 180 mg/dL	1.4	39.1	<0.001
% time in range 70-180 mg/dL	97.8	59.9	<0.001
CV	22.2	39.8	Not reported
Mortality rate (%)	6.2	28.8	<0.001
Length of stay (days)	4.3	5.7	<0.001

Table 1 – Summary of data from study noted in Figure 7. DM – Diabetes Mellitus, No DM – No Diabetes Mellitus, No UH – No Uncontrolled Hyperglycemia, UH – Uncontrolled Hyperglycemia. Bode, Journal of Diabetes Science and Technology, 2020.

In a recent study of 7,336 COVID-19 patients from China, it was demonstrated in a subgroup analysis of 500 matched type 2 diabetic patients that the group with well controlled glucose levels had a mortality hazard ratio of 0.14 (95% CI of 0.03,0.60) and an acute respiratory distress syndrome (ARDS) hazard ratio of 0.47 (95% CI of 0.27, 0.83) compared to the group with poorly controlled blood glucose levels (Figure 8). These results occurred despite the two groups having similar pulmonary CT findings at the time of admission. The Well Controlled glucose group had a median glucose of 6.4 mmol/L (5.2-7.5) versus 10.9 mmol/L (7.6-14.3) in the Poorly Controlled glucose group. For the overall study, the group with diabetes had a mortality rate of 7.8% versus 2.7% for the group without diabetes.[32]

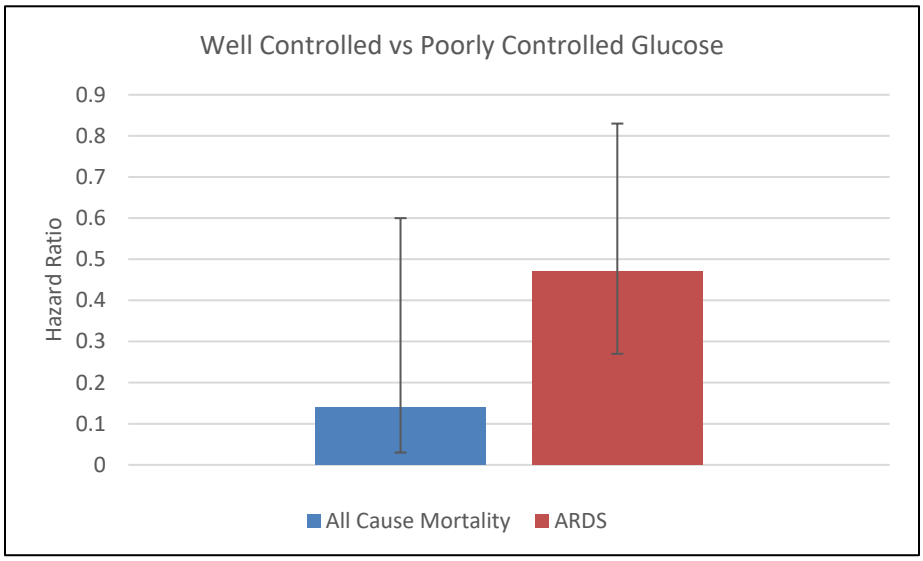


Figure 8 – Each group consisted of 250 matched type 2 diabetic patients with COVID-19 infection. Zhu, Cell Metabolism, 2020.

In a single hospital study of 403 consecutively admitted COVID-19 patients, it was shown that 57% of the COVID-19 patients developed hyperglycemia (>= 7.78 mmol/L).[33] This study noted that hyperglycemia in the first 24 and 48 hours of admission increased the mortality odds ratio by factors of 2.15 and 3.31. The presence of hyperglycemia showed statistical significance in predicting both ICU admission and the development of ARDS. Overall, 51 (12.7%) of the 403 hospitalized COVID-19 patients died in this study.

In a Spanish study, which used a nationwide registry from 109 hospitals, it was shown in a study of 11,312 COVID-19 patients that admission hyperglycemia was predictive of mortality in both diabetic and non-diabetic patients (Table 2).[34]

	Admission Glucose Level		
	< 140 mg/dL (N=8,870)	140-180 mg/dL (N=1,340)	>180 mg/dL (N=1,102)
Mortality Rate (%)	**15.7**	**33**	**41.1**
Number of Deaths	**1,394**	**442**	**453**

Table 2 – For the entire group, 61% of all deaths occurred in the group whose admission glucose levels were less than 140 mg/dL. Sanchez, Ann of Medicine, 2021.

This study is the largest COVID-19 study published to date, and while it points out the importance of using the admission glucose level to predict mortality rates in hospitalized COVID-19 patients, it should be noted that the majority of deaths occurred in the group of patients whose admission glucose levels were less than 140 mg/dL.

This points out the need to remain vigilant for the development of hyperglycemia after admission, in COVID-19 patients whose admission blood glucose levels are less than 140 mg/dL, as the previously noted study by Matmani demonstrated that the development of hyperglycemia within the first 24 and 48 hours of hospitalization has been associated with mortality (odds ratio 2.15 and 3.31, respectively).[33] The study by Matmani also demonstrated that non-diabetic patients admitted with COVID will often go on to develop hyperglycemia (e.g., > 140 mg/dL) after the first week of hospitalization (Figure 6), thus vigilance for the development of hyperglycemia may need to be extended throughout the entirety of their hospital stay.

In a study performed in Italy it was shown that the presence of hyperglycemia (>7.7 mmol/L) on admission significantly increases mortality rates in COVID-19 patients.[35]

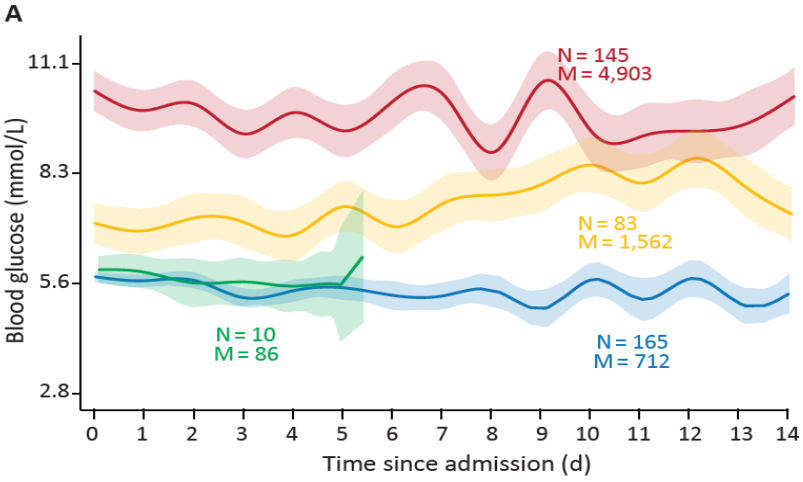


Figure 6 - This graph demonstrates that non-diabetic COVID-19 patients who develop hyperglycemia (e.g., > 140 mg/dL = 7.8 mmol/L), will often do so after their 7th day of admission (see yellow line above). The patients were divided into four groups based on their diabetes status (DM) and hyperglycemia (HG) status. Blue line represents no diabetes (DM-) and no hyperglycemia (HG-); yellow line no diabetes (DM-) but the presence of hyperglycemia (HG+); green line presence of diabetes (DM+) but no hyperglycemia (DM-); and red line presence of diabetes (DM+) and hyperglycemia (HG+). Matmani, MedRxiv, 2020.

In this same study it was shown that in the group of 25 patients with hyperglycemia on admission, a non-randomized subgroup who electively chose to be treated with intravenous insulin versus usual care with subcutaneous insulin, that the improved glucose control produced by use of an intravenous insulin infusion significantly decreased mortality rates (Figure 7). The patients treated with intravenous insulin had a target glucose range of 7.77 – 9.99 mmol/L. The patients treated with subcutaneous insulin received usual glucose control per their treating physician. The group treated with intravenous insulin were on the infusion for a mean of 32.7 ± 4.9 hours after entering the target glucose range of 7.77 – 9.99 mmol/L. After cessation of the intravenous insulin, this group of treated patients received usual glucose control with subcutaneous insulin per their treating physician.

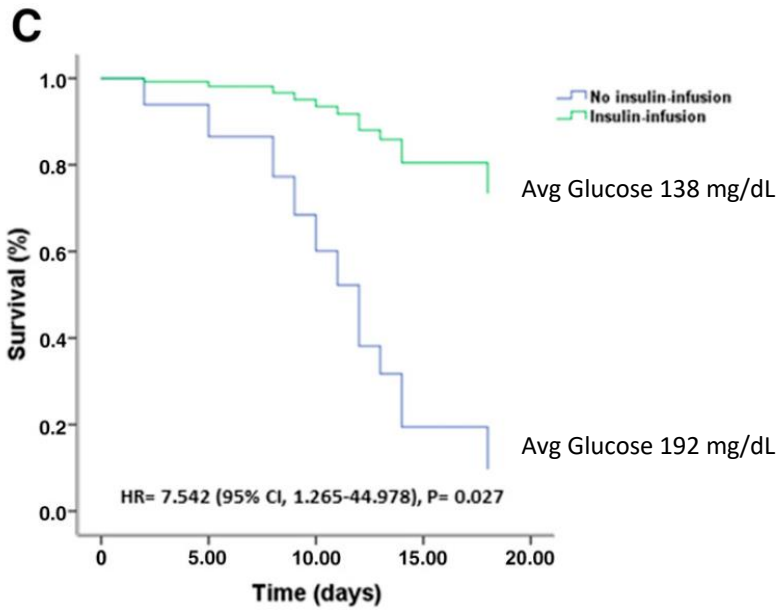


Figure 7 ***– Non-randomized initiation of insulin infusion in hyperglycemic (> 7.7 mmol/L on admission) COVID-19 patients. The No insulin infusion group were treated with subcutaneous insulin. Approximately 70% of patients in each group had diabetes. Sardu, Diabetes Care, 2020.***

One explanation for the improved outcomes in the patients treated with an intravenous insulin infusion may be a reduction in their inflammatory state and a reduction in their propensity to form blood clots, which are two common and most likely related conditions seen in COVID-19 patients.[36-38]

Previous animal models of lung injury have confirmed that elevated blood glucose levels exacerbate lung inflammation, and that lowering of the blood glucose level with insulin effectively minimizes the degree of induced lung inflammation and edema based on wet lung weight, lung inflammatory markers, and on pathological specimens.[39-41] These results have been confirmed in human studies that demonstrated the ability of acute hyperglycemia to induce increased cytokine levels.[42] Furthermore, increased cytokine levels have been implicated in the development of ARDS in COVID-19 patients.[43]

Finally, a laboratory study showed that when human peripheral monocytes are infected with CoV-2 (COVID-19), the viral load of the monocytes after 24 hours of incubation in glucose containing medium was logarithmically related to the glucose level of the medium the monocytes were incubated in.[44] This

same laboratory study noted a similar effect on expression of the pro-inflammatory cytokine IL-1β, which has been shown to be an important mediator of the cytokine storm seen in COVID-19 patients.[45] Although the optimal glucose control range for critically ill COVID-19 patients is unknown, a recent multi-center study demonstrated that average ICU glucose levels greater than 140 mg/dL increased COVID-19 mortality rates by almost 100% (Table 3).[46] In this same study, a multivariable Cox regression analysis was conducted to assess predictors of ICU mortality. Age older than 60 (HR:3.21 [95% CI 1.78, 5.78]) and hyperglycemia with mean ICU glucose >140 mg/dL (HR:1.79 [95% CI 1.14, 2.82]) were the only two predictors of increased ICU mortality.

	Average ICU glucose < 140 mg/dL (n=242)	**Average ICU glucose >= 140 mg/dL (n=253)**	**p Value**
Mortality rate (%)	16.6	31.4	< 0.001
Mechanical Ventilation (%)	37.2	50.0	<0.004
ICU LOS	3.5	5.5	< 0.001

Table 3 – Diabetes present in 38.5% of entire cohort. For the entire cohort, the mean value of blood glucose at the time of admission was 186.6 mg/dL (SD+130.8). Saand, J Diabetes, 2020.

To date, most attempts to control the glucose level of COVID-19 patients have met with only marginal success, as their glucose levels are highly variable and nonlinear, making them difficult to control using the current open loop techniques. In a retrospective analysis of 562 ICU admissions at a single medical center, the patients with COVID-19 had statistically significant worse glucose control, versus non-COVID-19 ICU patients, despite attempts to control their glucose levels with the FDA approved GlucoStabilizer insulin dosing software program (Table 4).[47]

Outcome	In Sample (562)	COVID-19 (93)	Non-COVID-19 (469)	*p*-Value
Insulin use (daily average) [a]	7.63 (4.65)	8.37 (4.08)	6.17 (5.30)	<0.001
Glucose Time in Range (%)				
<70 mg/dL	0.44	0.44	0.44	<0.001
70–150 mg/dL	60.13	44.42	68.52	
151–250 mg/dL	33.31	43.48	27.88	
>250 mg/dL	6.12	11.66	3.16	
Glucose mg/dL				
Mean (SD)	150.89 (60.51)	170.59 (66.60)	140.37 (54.13)	<0.001
Median (IQR) [a]	136 (112–174)	157 (124–205)	130 (107–159)	
Coefficient of Variation in Glucose level	0.40	0.39	0.38	
Peak Glucose mg/dL				
Mean (SD)	190.31 (98.79)	243.07 (122.62)	179.18 (89.25)	<0.001
Median (IQR) [a]	164 (130–218.5)	215 (146–323)	160 (128–201.5)	
Mortality *n* (%)	85 (15.12)	20 (21.51)	65 (13.86)	0.06

[a] Wilcoxon Rank-Sum (Mann–Whitney) test.

Table 4 – Table is from retrospective data analysis study comparing glucose control in ICU patients both with (n=93) and without (n=469) COVID-19. The ICU patients with COVID-19 had statistically significant lower percent time in range 70-150 mg/dL, compared to non-COVID-19 ICU patients. Kapoor, Journal of Clinical Medicine, 2020.

A multi-center retrospective analysis of 1,122 hospitalized COVID-19 patients demonstrated the importance of attempting to achieve good glucose control in this patient population. The group of patients with either diabetes or uncontrolled hyperglycemia had statistically significant worse glucose control (Table 5) and higher mortality rates. Inadequate glucose control occurred in the Diabetic and Uncontrolled Hyperglycemia group despite use of the FDA approved Glucommander insulin dosing software program.[31]

Variable	+ Diabetes and/or Uncontrolled Hyperglycemia (n=451)	- Diabetes or Uncontrolled Hyperglycemia (n=671)	p-value
BG Events, n (%)	19168	6532	
Mean Glucose, mg/dl (SD)	178.5 (±71.0)	116.6 (±25.9)	<0.001
BGs > 250 mg/dl, n (%)	2795 (14.6)	6 (0.1)	<0.001
BGs > 180 mg/dl, n (%)	7499 (39.1)	91 (1.4)	<0.001
BGs 70-180 mg/dl, n (%)	11473 (59.9)	6389 (97.8)	<0.001
BGs < 70 mg/dl, n (%)	196 (1.0)	52 (0.8)	0.106
BGs < 54 mg/dl, n (%)	69 (0.4)	10 (0.2)	0.009
BGs < 40 mg/dl, n (%)	31 (0.2)	4 (0.1)	0.057
Patient Days, n (%)	3885 (50.6)	3793 (49.4)	
Patient Days with Mean BG > 180 mg/dl, n (%)	1470 (37.8)	46 (1.2)	<0001
Patient Days with at least 1 BG > 250 mg/dl, n (%)	1004 (25.8)	6 (0.2)	<0.001
Patient Days with at least 1 BG > 180 mg/dl, n (%)	2252 (58.0)	91 (2.4)	<0.001
Patient Days with at least 1 BG < 70 mg/dl, n (%)	137 (3.5)	39 (1.0)	<0.001
Patient Days with at least 1 BG < 54 mg/dl, n (%)	63 (1.6)	16 (0.4)	<0.001
Patient Days with at least 1 BG < 40 mg/dl, n (%)	25 (0.6)	3 (0.1)	<0.001

Table 5 – Glucose data from retrospective analysis of 1,122 patients with COVID-19. The group of patients with either Diabetes or Uncontrolled Hyperglycemia (two glucose values > 180 mg/dL in any 24-hour period) had statistically significant worse glucose control despite use of an FDA approved insulin dosing software program (Glucommander). Bode, Journal of Diabetes Science and Technology, 2020.

In these open loop systems, the nurse manually checks the patient's blood glucose level every 1-4 hours, enters the measured level into the insulin dosing software, and then manually enters the results of the insulin dosing software into the insulin infusion pump as depicted below (Figure 11). These systems do not utilize a dextrose (D-glucose) component for purposes of control, which makes them prone to periods of hypoglycemia.

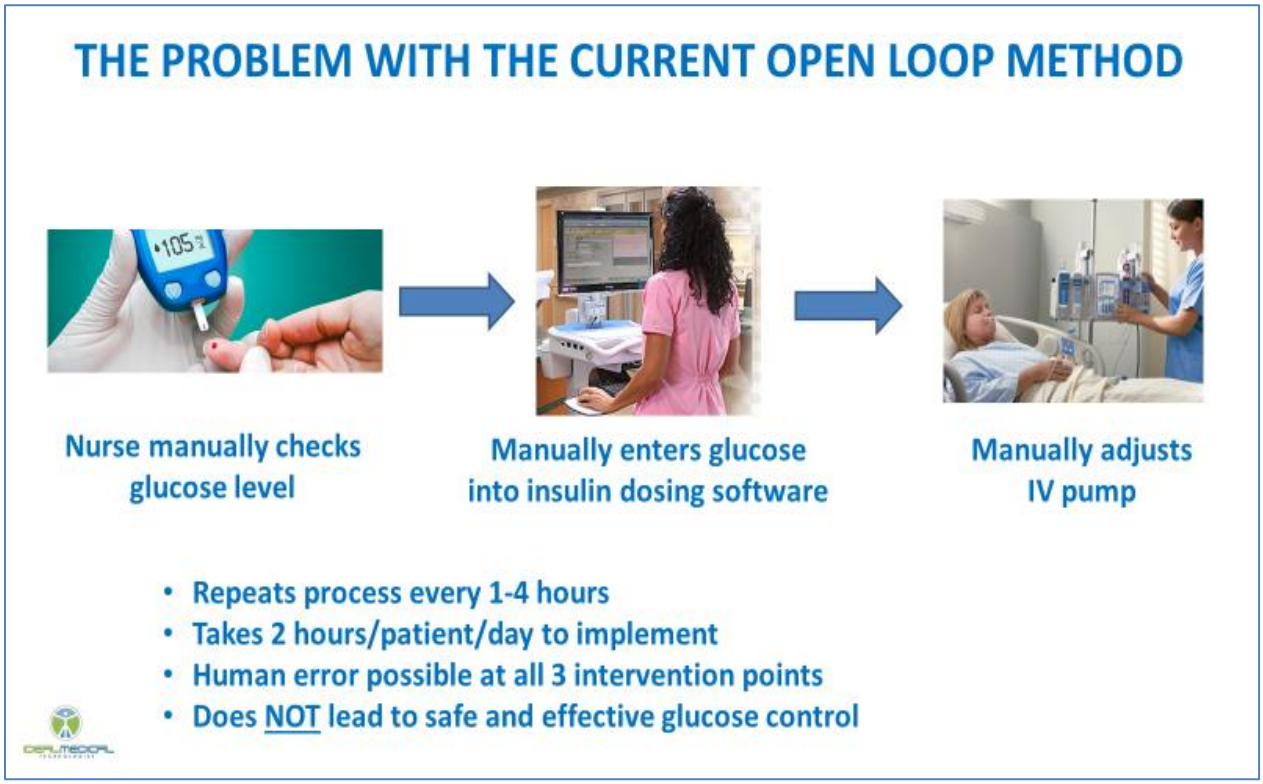


Figure 11 – Depiction of the current process of glucose control in the ICU setting using an open loop method.

With use of the current open loop glucose control technique ICU patients still experience high rates of hypoglycemia, hyperglycemia, low time in the desired glucose range, and large glucose variability.[48]

In the U.S., as of June, 2022, there have been more than 88 million cases and over 1 million deaths due to COVID-19. Given that the new BA.5 COVID variant is driving a new wave of infections in the U.S., with currently more than 30,000 patients hospitalized, and the potential for tight glucose control to lower mortality rates in hyperglycemic COVID-19 patients both with and without diabetes, development of a safe and effective closed loop glucose control system intended for use in COVID-19 patients is urgently needed.

2.3 STUDY RATIONALE – FUSION AI BASED ARTIFICIAL PANCREAS SYSTEM

The novel glucose control system to be tested in this study is an expert based rule system or Knowledge Based System.[49,50] This system should be considered a form of artificial intelligence, whose main goal is to completely model the natural glucose homeostatic system. The essential elements of the native

glucoregulatory system, which were used to create the AI based system under study, have been reviewed[51] by Dr. Leon DeJournett, who is the developer of the novel AI based glucose controller to be tested in this study. If successful, this controller could be utilized in a closed loop glucose control system (artificial pancreas) for treatment of dysglycemia in ICU patients.

Through an intensive review of how the native glucose control system functions (e.g., pancreas & liver), a knowledge based multiple input multiple output (MIMO) glucose control system has been developed.[52] **The algorithms of this system use the four input variables of absolute glucose, glucose rate of change, weight based intravenous insulin dose and weight based intravenous dextrose dose.** Based on the values of these four input variables and the desired glucose control range, the two output variables of continuous intravenous insulin and continuous intravenous dextrose are adjusted. The results from the primary knowledge-based controller are also run through additional knowledge based controllers. These additional controllers monitor for outlying situations such as rapid falls or rise of blood glucose levels. These controllers will modify the two output variables from the primary controller if the clinical situation warrants such a change. Through utilization of the proper control techniques and frequent adjustment of the insulin and/or dextrose infusion rates (every 5 or 10 minutes), tight control of glucose will be achieved. In addition, episodes of clinically significant hypoglycemia will be avoided, and glucose variability will be minimized.

The20lucosn for continuing clinical studies at this time is that thorough preclinical studies and a small first in human study of this controller have already been completed. The preclinical studies included the largest simulation study of a glucose controller published to date,[53] and a comparative simulation study that showed clear superiority of the AI based controller over Glucommander and several other ICU based glucose controllers.[54] In addition, non-Good Laboratory Practice (GLP) animal testing using a swine model of stress induced hyperglycemia[55] showed that the controller was able to achieve tight glucose control with no significant hypoglycemia.[56] In a second larger animal study the artificial pancreas (AP) system demonstrated its ability to avoid severe hypoglycemia and minimize moderate hypoglycemia despite having to deal with an unannounced intravenous insulin injection.[57] Finally, in a two subject first in human study on type 2 diabetic subjects in a CRC setting, the controller was able to maintain a high percent time in range 70-180 mg/dL while avoiding any hypoglycemia (< 70 mg/dL).

3 FUSION SYSTEM TESTING BACKGROUND

The testing to date of the AI based glucose controller under study includes two simulation studies, two animal studies, and a first in human study on two subjects.

3.1 SIMULATION STUDIES

Both simulation studies used a mathematical model of the ICU patients glucose-insulin system that has been clinically validated.[58] The two AI controller outputs of insulin and dextrose were incorporated into the model, such that the controller's outputs could attempt to bring control to the modelled system as the system experienced time variant changes of its internal parameters, or was perturbed through time variant exogenous infusions of intravenous dextrose.

In the first simulation study, ICU "patients" were created through use of time variant changes in their insulin sensitivity, volume of distribution and half-life. In addition, variable rates of dextrose infusions were used to simulate potential clinical scenarios. The glucose sensor data also had variable degrees of accuracy ranging from 5-15%, and bias ranging from ± 0-10 mg/dL. Finally, three different starting glucose values and seven different control ranges were used. This led to 126,000 unique simulations, each done over a period of five days. This study produced 15 million hours of simulation time and 107 million glucose values for analysis.[53] As can be seen below (Figure 12), when the control range was set to 100-140 mg/dL and the sensor error was 10%, the time in range of 70-140 mg/dL was 95%, which is consistent with the "time in range hi" group noted above (Figure 1).

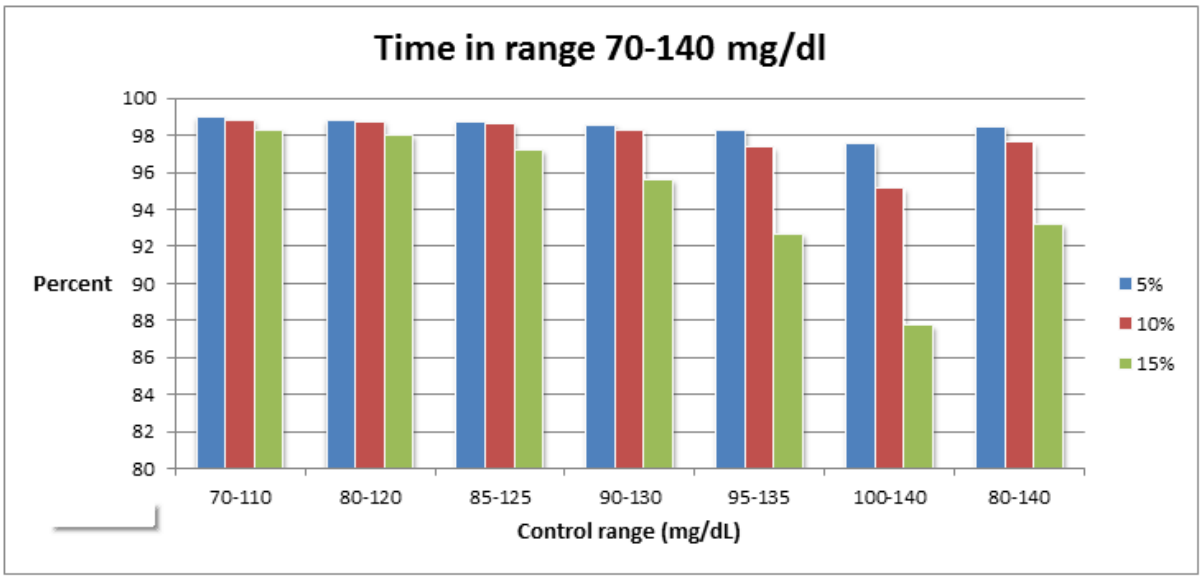


Figure 12 – SE = sensor error. DeJournett, Journal of Diabetes Science and Technology, 2016.

The controller also did an exceptional job of avoiding any significant hypoglycemic events with an overall rate of hypoglycemia (< 70 mg/dL) of 0.09% with a sensor error of 10% as noted below (Figure 13). By adjusting the desired control range, clinicians can easily adjust the hypoglycemia rate towards zero, as was seen in the 100-140 mg/dL control range group. For the entire study there were no glucose values less than 45 mg/dL.

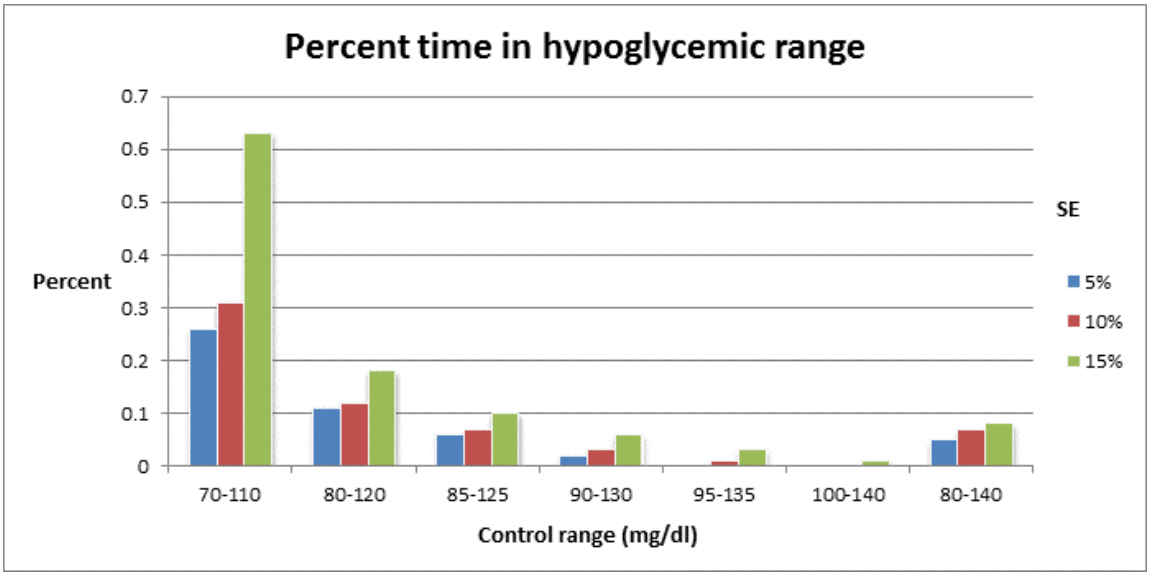


Figure 13 –Hypoglycemia defined as < 70 mg/dL. SE = sensor error. DeJournett, Journal of Diabetes Science and Technology, 2016.

As seen below (Figure 14), the controller was just as adept at minimizing glucose variability as noted by an average CV of 11.1% when the sensor error was 10%. The ability to minimize glucose variability to this degree should have a significant impact on ICU mortality rates as evidenced by the clinical results shown in Figure 2 above.

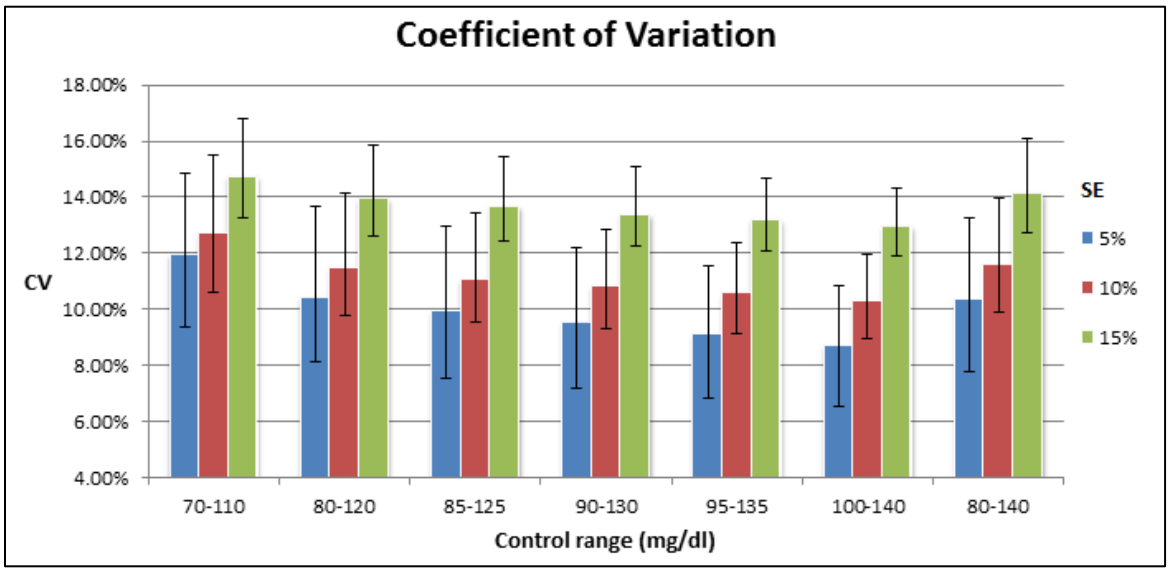


Figure 14 – ***SE = sensor error. DeJournett, Journal of Diabetes Science and Technology, 2016.***

In a second simulation study the same mathematical model and time variant changes were used to create 80 virtual "patients," and a novel random walk sensor error method was used that guaranteed an overall sensor error of 10%. This study utilized five, time variant exogenous dextrose infusions to perturb the model and produced a total of 400 five-day simulations per controller. The AI controller to be tested in the current study,[52] which is being commercialized by Ideal Medical Technologies (IMT), was compared to the Yale protocol (YALE),[59] Glucommander (GLUC),[60] Wintergerst et al PID controller (PID),[61] GRIP,[62] and the NICE-SUGAR (NICE) study protocol[63] in a comparative simulation study.[54] Seen below (Table 6) is a summary of the results from this study.

	Severe Hypoglycemia Incidence (%)	Mild Hypoglycemia (40-69 mg/dL)	Control range (100-140 mg/dL)*	Normoglycemia (70-140 mg/dL)	CV (%)
IMT	**0.00**	**0.00 (0.00-0.00)**	**92.6 (89.8-96.2)**	**96.7 (94.6-97.9)**	**9.9 (8.4-11.5)**
Yale	0.25	0.81 (0.00-1.61)	64.1 (54.3-72.7)	71.5 (63.8-77.7)	18.3 (15.1-21.2)
Glucommander	4.50	1.63 (0.82-3.23)	67.6 (57.6-76.4)	78.0 (70.7-84.1)	18.2 (14.7-21.5)
PID	4.50	0.80 (0.00-2.43)	63.8 (52.5-71.2)	75.7 (67.8-81.4)	19.1 (15.9-22.3)
GRIP	6.25	1.66 (0.00-3.01)	65.1 (51.3-75.9)	76.1 (65.6-83.8)	19.0 (14.7-22.0)
NICE	2.50	3.97 (0.00-6.40)	42.8* (33.6-52.6)	89.0 (80.9-95.1)	20.6 (17.0-24.2)

Table 6 – Values are median (25-75) percent of all glucose values in given range and CV., Severe hypoglycemia is percent of simulations. *NICE results are for time in range 81-108mg/dL. DeJournett, Journal of Diabetes Science and Technology, 2017.

As can be seen from Table 6 the IMT AI based controller showed clear superiority in this simulation study. It is important to note that the IMT controller achieved a time in range 70-140 mg/dL greater than 95%, a CV less than 15% and a hypoglycemia rate of 0. Per the previous noted clinical studies, all these results will correlate with improved survival of ICU patients, if they carry over to the real world setting.

3.2 ANIMAL STUDIES

Although the FDA does accept simulation testing as a sole valid method to accomplish pre-clinical testing of glucose controllers,[64-66] it was decided to perform two animal tests to assess the performance of IMT's complete closed loop glucose control system in an in vivo setting. In the first small pilot animal

study a fully functional closed loop glucose control system, which is essentially the same system to be tested in the current proposed study, was utilized to complete a twelve hour closed loop glucose control study in a swine model of stress induced hyperglycemia.[56] For this study the stressors to the anesthetized swine included endotoxin infusion to mimic sepsis,[67] lung aspiration of hydrochloric acid to mimic acute respiratory distress syndrome,[68] and a high dose of Solumedrol to mimic the stress hormone response seen in critically ill patients.[69] The animals also received dextrose boluses to elevate their24lucosee Levels at the start of the experiment, and high rates of dextrose infusions (5-10 mg/kg/min) to make glucose control difficult to achieve. In one scenario, the animals were under type 1 diabetes conditions through infusion of Octreotide,[70] with C-peptide levels confirming lack of native insulin production.

As noted below (Figure 15), the fully functional artificial pancreas (AP) system was able to maintain the blood glucose level in a normal swine range of 40-80 mg/dL in the animals that were rendered type I diabetics via an Octreotide infusion[56] and simultaneously were in a state of stress induced hyperglycemia (SIH). While it is not surprising that the control animal that did not receive any insulin died, the important point is that the treated animal was able to achieve effective tight glucose control which produced a lower stress state as noted by a normal lactic acid level.

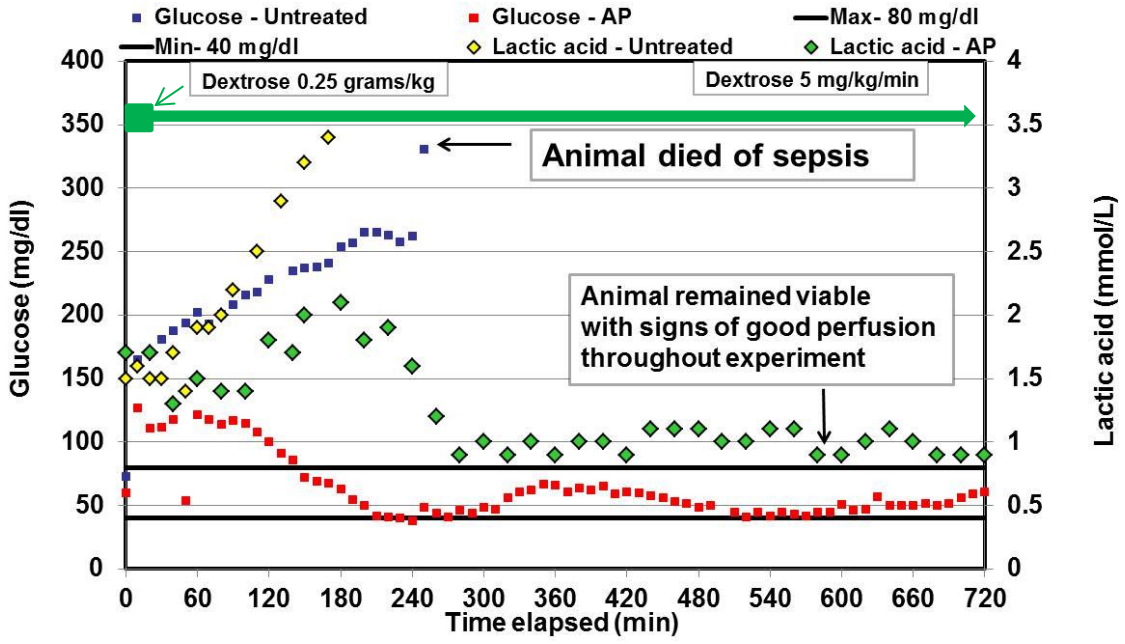


Figure 15 – Dextrose bolus of 0.25 grams/Kg given at time 0, and dextrose infusion of 5 mg/kg/min from time 0-12 hours. AP = artificial pancreas. Octreotide infusion used to create a type I diabetic state in both animals. DeJournett, Diabetes, 2016.

As can be seen below (Figure 16), IMT's AI based glucose control system was just as effective in augmenting the animal's intact endogenous insulin production. Although the control animal was unable to bring its glucose level into the normal range throughout the course of the twelve hour experiment, **IMT's AI based controller was able to bring the glucose level into the desired range within 4 hours**, and maintain it within or close to the desired range throughout the rest of the experiment. It should also be noted that the untreated animal had elevated lactic acid levels compared to the animal that achieved effective tight glucose control with IMT's AP system.

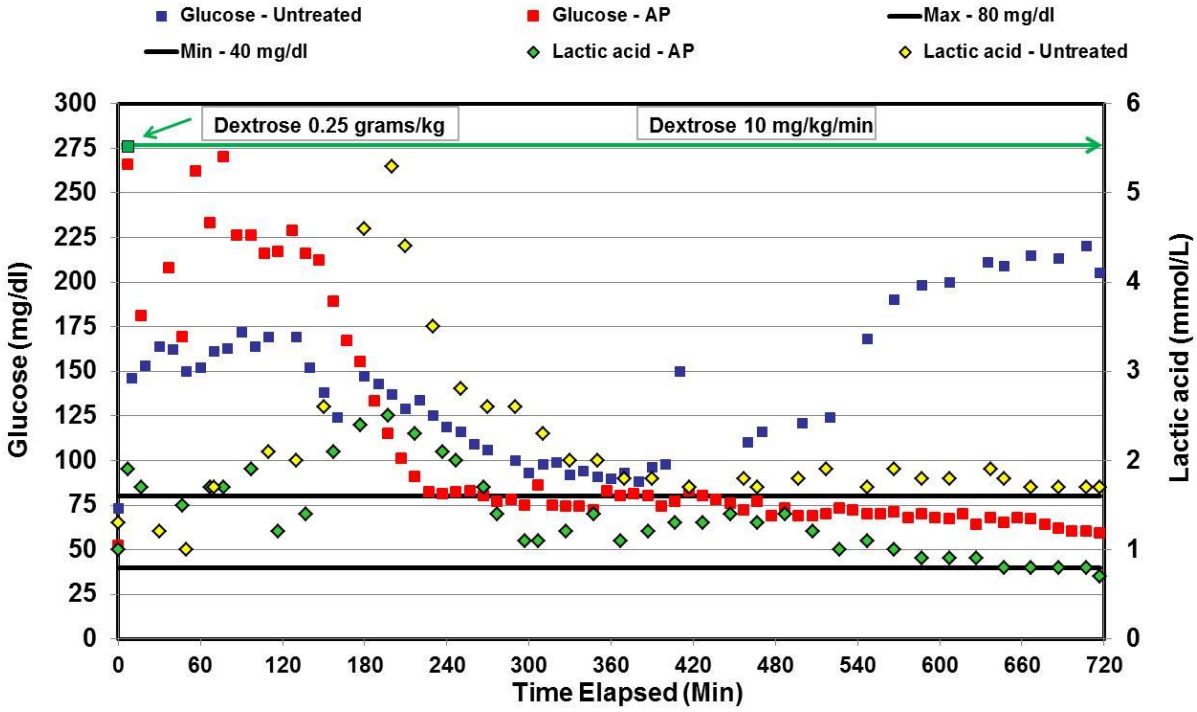


Figure 16 – Dextrose bolus of 0.25 grams/Kg given and time 0, and dextrose infusion of 10 mg/kg/min from time 0-12 hours. AP = artificial pancreas. Both animals had their endogenous insulin production left intact. DeJournett, Diabetes, 2016.

In the second animal study the safety and performance of the FUSION system was assessed using a swine model of unannounced hypo- and hyperglycemia challenges. For this test the FUSION system was composed of the EIRUS (Getinge AB) CGM, which is a CE marked CGM designed for use in the ICU setting, the FUSION systems artificial intelligence-based (AI-based) glucose control software, and two syringe pumps. The study protocol is seen below (Figure 17).

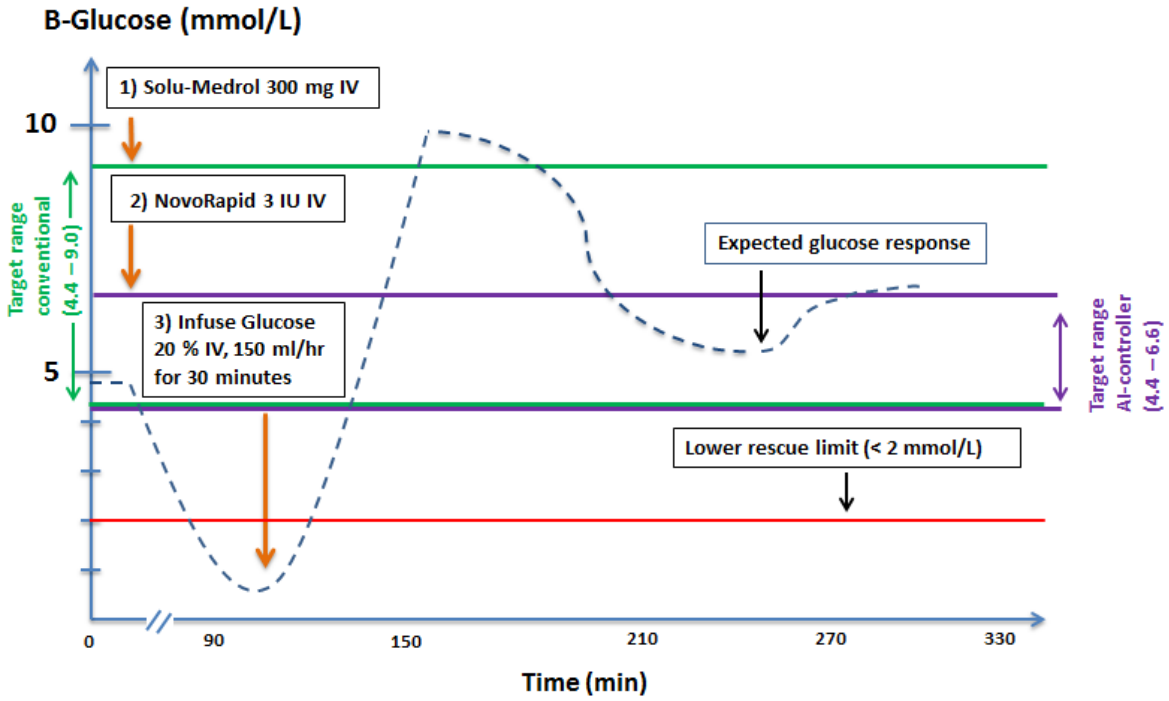


Figure 17 – Protocol format. The ICU physician attempted to control to the range of 4.4 – 9 mmol/L, while the FUSION artificial pancreas system attempted to control to the tighter range of 4.4 – 6.6 mmol/L. The protocol was designed to induce hypoglycemia with a bolus of 3 units of insulin at time 20 minutes, and unavoidable hyperglycemia with a glucose infusion of 17 mg/kg/min from time 110 – 140 minutes as a means to test the artificial pancreas systems ability to avoid severe hypoglycemia after an unannounced insulin overdose and delayed moderate hypoglycemia secondary to treatment of the induced hyperglycemic state. DeJournett, Journal of Clinical Monitoring and Computing, 2020.

The results from the fully autonomous FUSION system were compared to an ICU physician who had access to every 30-minute arterial glucose values and who used Dextrose 20% and NovoRapid to treat hypoglycemia and hyperglycemia. Both the control and treated animals had EIRUS CGM's in place, and the glucose values from these CGM's were used for statistical comparison. Noted below (Figure 18) are the median (25-75) glucose values from both groups. As can be seen from this graph the FUSION system, acting in a fully autonomous mode, was able to avoid both severe hypoglycemia after the insulin bolus and rebound moderate hypoglycemia secondary to treatment of the induced hyperglycemic state. The ICU physician, despite having access to every 30-minute arterial blood glucose values, was unable to avoid severe and moderate hypoglycemia.

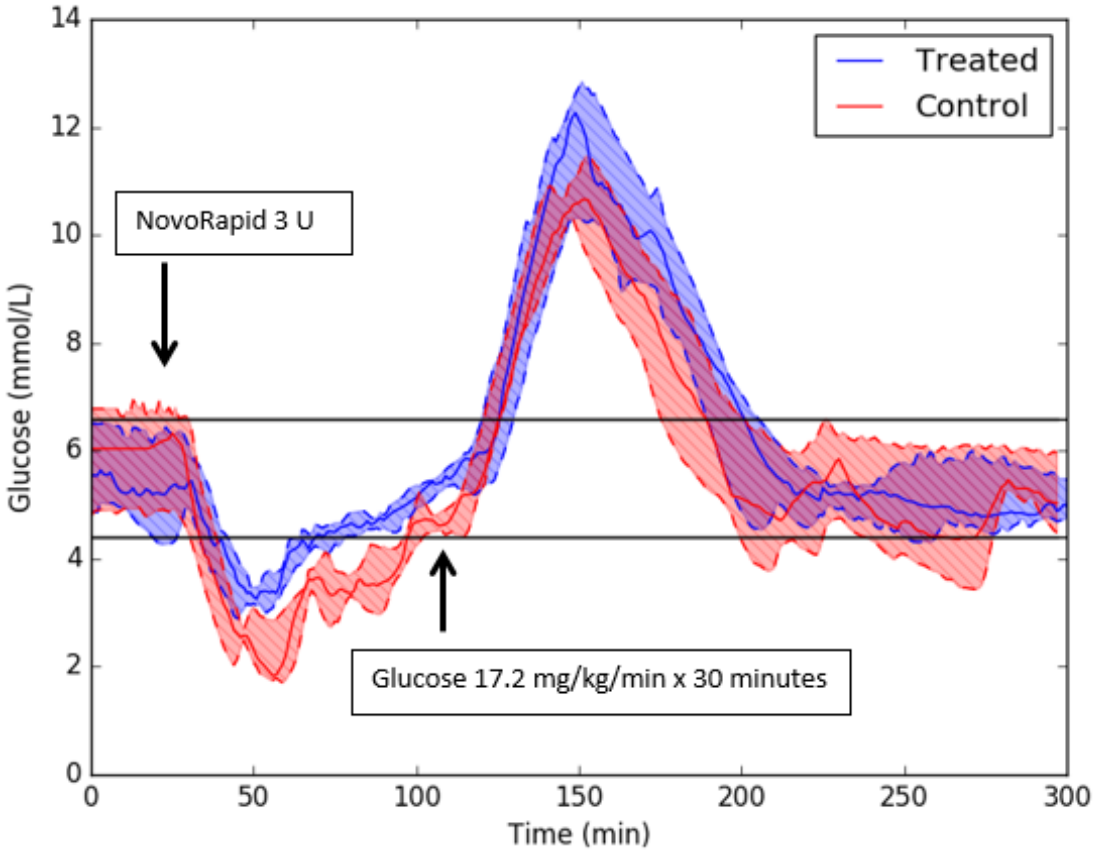


Figure 18 – Median (25-75) glucose values from both groups. The FUSION artificial pancreas system had an improved safety profile despite controlling to the tighter range of 4.4 – 6.6 mmol/L. Treated = FUSION system, Control = ICU physician.

Noted below (Table 7) is the performance of the FUSION system in the hypoglycemic range (<3.5 mmol/L). It should be noted that none of the "Treated" animals experienced severe hypoglycemia and that all other measures related to hypoglycemia were significantly improved by the fully autonomous artificial pancreas system, despite the fact it was controlling to a tighter range which should have led to a higher rate of hypoglycemia as noted above (Figure 13). This study provides proof that an autonomous glucose control system that adjusts the rates of insulin and/or glucose infusions every 5-10 minutes should be able to outperform a bedside ICU physician, even when the physician has access to every 30-minute arterial blood glucose values.

Hypoglycemia Statistics	Treated (N = 8)	Control (N = 6)	p value
Number of animals with severe hypoglycemia†	0	5	<0.003*
Minimum glucose (mmol/L)	2.83 (2.75-2.96)	1.69 (1.68-1.89)	0.033*
Total time in hypoglycemia for all events (minutes)	12.5 (10.5-16.0)	41.0 (33.5-61.3)	<0.004*
Mean of all hypoglycemic glucose values (mmol/L)	3.20 (3.07-3.24)	2.80 (2.43-2.87)	<0.033*
Longest singular hypoglycemic event (minutes)	9.5 (8.8-11.3)	24.5 (20.8-29.8)	<0.012*
AUC†† 3.5mmol/L (mmol/L * minutes)	4.8 (3.1-5.2)	28.9 (21.1-54.2)	<0.004*
AUC†† 2.2mmol/L (mmol/L * minutes)	0.0 (0.0-0.0)	3.6 (1.3-5.2)	<0.004*

Table 7 – Hypoglycemia defined to be glucose less than 3.5mmol/L. All continuous data are reported as median (25-75). All glucose data, and not just the data from the induced hypoglycemia episode from time 20min to time 110min, were considered in these statistics. Statistical significance (p<0.05) indicated by *. A "hypoglycemic event" is defined as a sequence of hypoglycemic blood glucose values that is contiguous in time, terminated on both ends by a non-hypoglycemic value. † If an animal experienced any values less than 2.22mmol/L, it was counted as having experienced severe hypoglycemia – comparison made using the Fisher's exact test. ††Area under the curve (AUC); area accumulated while glucose was less than this threshold.

3.3 HUMAN STUDY

The first in human study on two subjects was performed in the clinical research center (CRC) of Emory University under the direction of Dr. Francisco Pasquel. This study was performed on subjects with type 2 diabetes who had no underlying end organ disease, used insulin at home to treat their diabetes, and whose HbA1c was in the range of 7-10%. The FUSION system attempted to control their glucose level to a range of 100-140 mg/dL for a period of 24 hours. The subjects at three standardized meals during this 24 hour period, with the first meal consumed being lunch. The subjects were also allowed to eat snacks from 2100 to 0600 hours. For safety reasons, the subjects had an independent reference glucose checked every 10-60 minutes using either a YSI glucose analyzer or the Nova StatStrip Hospital Glucose

Meter System point of care glucose meter. The two subject's demographic data is noted below (Table 8).

	Subject 1	**Subject 2**
Age, years	37	40
Sex, M/F	F	F
Weight, Kg	149.7	114.6
BMI, (kg/m^2)	47.7	39.6
Race	African American	Caucasian
Ethnicity	Non-Hispanic	Hispanic
Diabetes duration, years	4	20
Home Diabetes Treatment		
Total daily insulin, U/day	155	54
Total daily insulin, U/kg	1.04	0.47
Total Basal Insulin, U/day	80	28
Prandial Insulin, U/day	75	28
OAD, y/n	Y	Y
Baseline Labs		
Glucose, mg/dL	162	197
HbA1c, %	8.2	8.2
Cr, mg/dL	0.88	0.55
GFR, mL/min/1.72m^2	88	118
Hb, g/dL	13.8	12.3
ALT, unit/L	13	13
AST, unit/L	14	13
Na, nmol/L	142	138
K, nmol/L	3.9	4.0

Table 8 – Demographic data for the two subjects from the first in human trial of the FUSION system.

The glucose metrics and weight based infusion rate data from the two subjects are seen below (Table 9).

	Subject 1	**Subject 2**	**Average (SD)**
% TIR < 70 mg/dL	0	0	0
% TIR 70-140 mg/dL	88.7	76.4	82.6 (6.2)
% TIR 100-140 mg/dL	78.1	60.6	69.4 (8.8)
% TIR 70-180 mg/dL	100	94.5	97.3 (2.7)
% TIR > 180 mg/dL	0	5.5	2.7 (2.7)
Coefficient of Variation (%)	13	26	19.7 (10)
Mean Glucose (mg/dL)	121	125	123 (2)
Average insulin infusion rate (U/Kg/hr)	0.044	0.038	0.041 (0.005)
Average glucose infusion rate (mg/Kg/min)	0.39	0.62	0.50 (0.16)

Table 9 – Glucose metrics and infusion rate data from first in human study of FUSION system. SD – Standard deviation.

The 24 hour glucose versus time graphs from the two studies can be seen below (Figure 19).

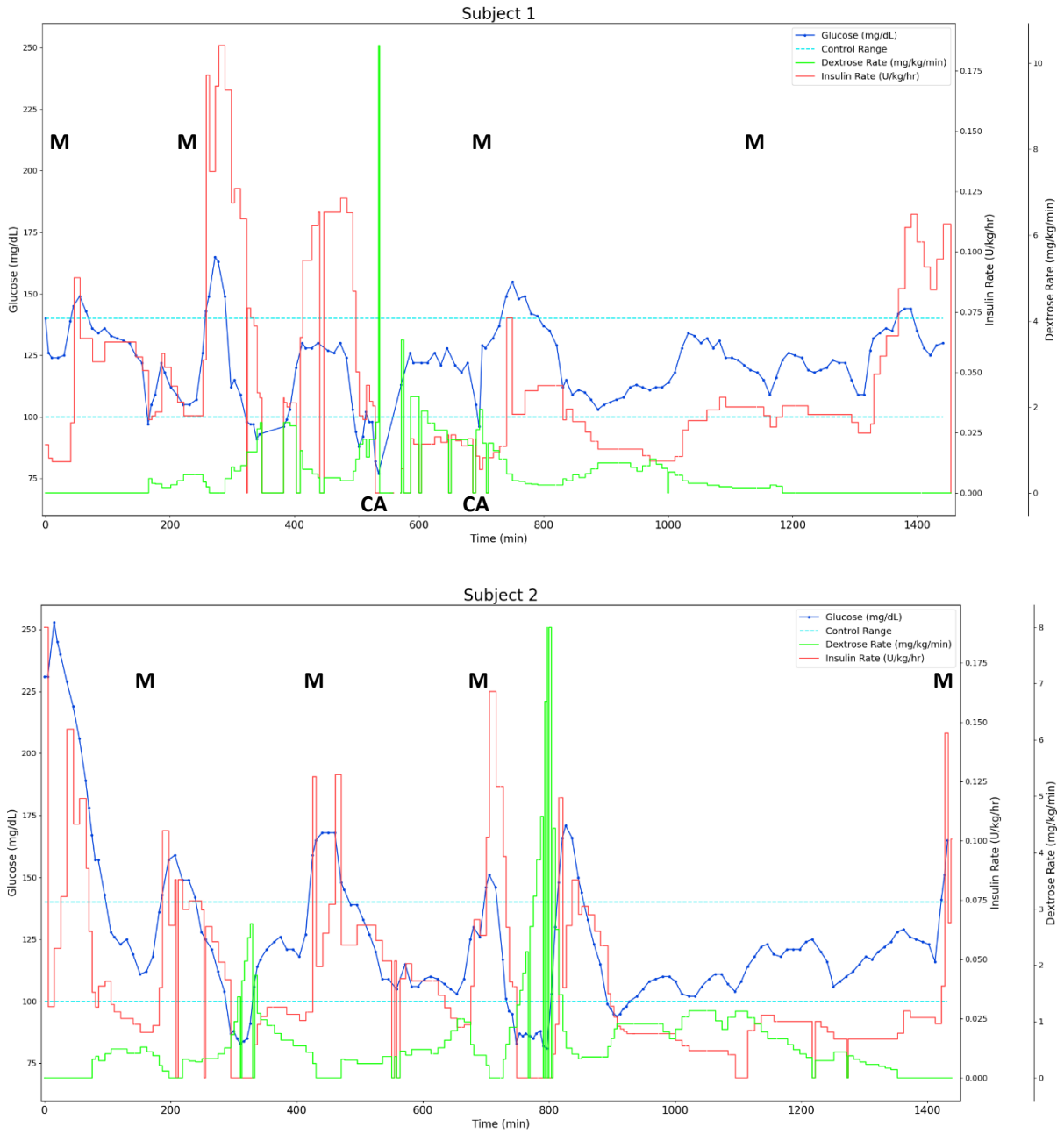


Figure 19 – Glucose vs time plots with overlayed weight based insulin and dextrose infusion rates for subjects 1 and 2. M – Meal or snack. CA – Compression artifact secondary to subject lying directly on Dexcom G6 CGM sensor. Gaps in infusion rate data (e.g., Insulin infusion Subject 1 at times 400 & 450 minutes) represent FUSION system pauses for syringe changes or CGM calibration.

The medical device to be tested in this proposed CRC study is a fully functional closed loop glucose control system and is pictured below (Figure 20).

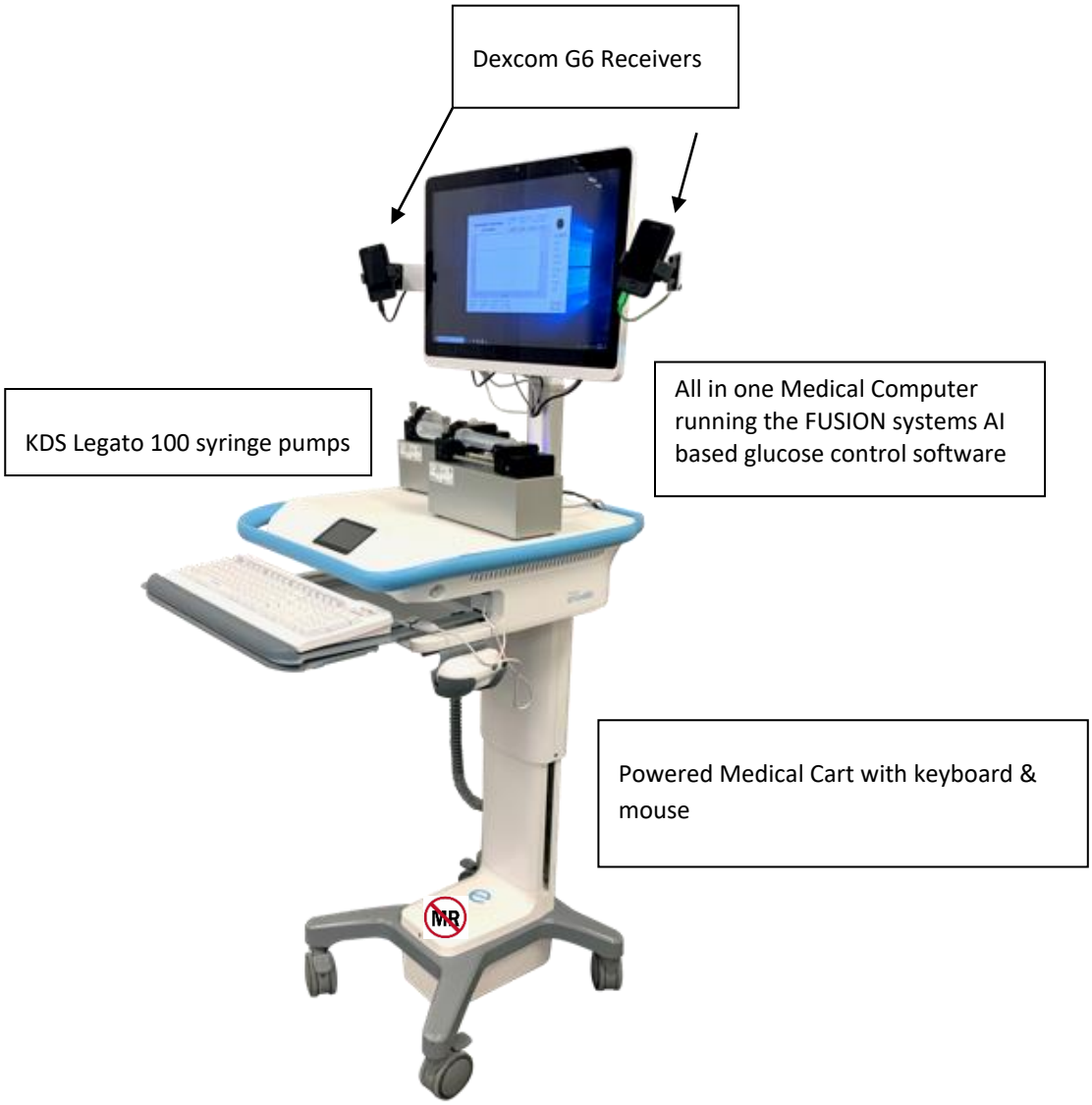


Figure 20 – Pictured is the prototype of the FUSION device. The FUSION systems AI based glucose control software (Controller) is run on an all in one Medical Computer (Teguar) that is mounted on the powered Medical Cart (Enovate). This picture shows KDS Legato 950 OEM syringe pumps, but the study will be done with KDS Legato 100 syringe pumps.

A screen shot of the glucose control software is shown below (Figure 21).

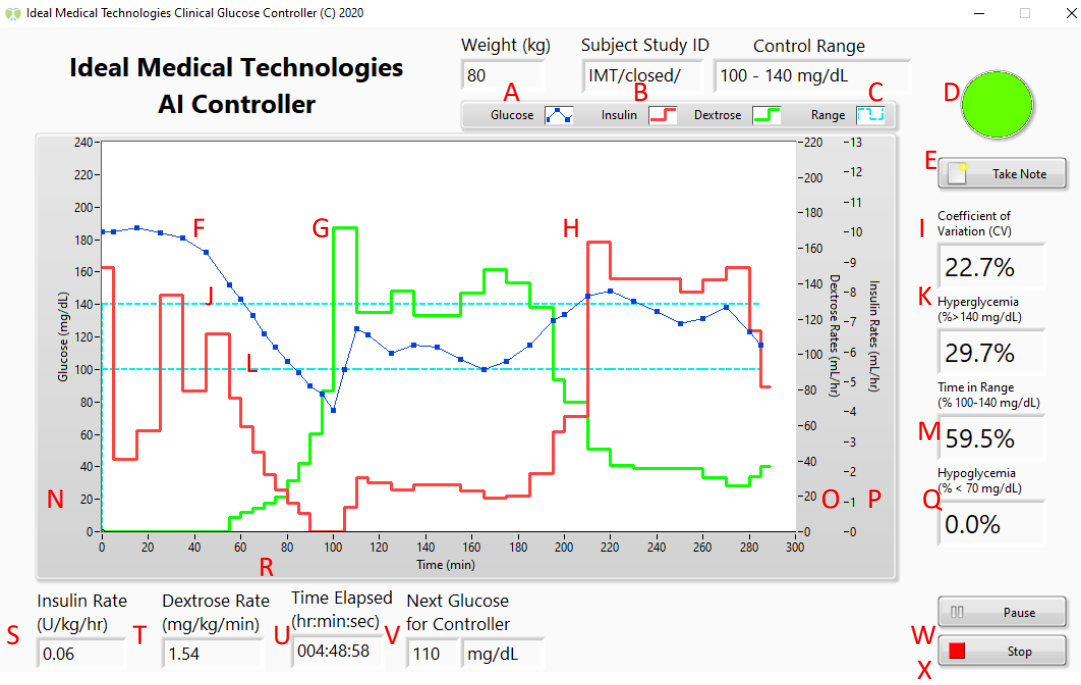


Figure 21 – Screenshot of active glucose control software.

A	Patients weight in kg.
B	Unique identification number of study patient.
C	Glucose control range used for study in mg/dL.
D	Flashing green circle indicating software is functioning normally.
E	Note entry button – allows for entry of notes related to use of FUSION system.
F	Glucose versus time curve (blue line).
G	Dextrose infusion rate curve (green line). See right Y-axis for rate.
H	Insulin infusion rate curve (red line). See right Y-axis for rate.
I	Coefficient of variation statistic.
J	Upper limit of glucose control range (dashed light blue line).
K	Percent time in hyperglycemic range (> 140 mg/dL).
L	Lower limit of glucose control range (dashed light blue line).
M	Percent time in glucose control range (100-140 mg/dL).
N	Y axis (Glucose level in mg/dL).
O	Dextrose infusion rate (mL/hr).
P	Insulin infusion rate (mL/hr).
Q	Percent time in hypoglycemic range (< 70 mg/dL).
R	X-axis (Time in minutes).
S	Insulin infusion rate (U/kg/hr).
T	Dextrose infusion rate (mg/kg/min).
U	Total time elapsed since start of study (hours:minutes:seconds).
V	Next glucose value to be used by controller for purposes of glucose control.
W	Pause button to temporarily stop FUSION system.
X	Stop button to permanently stop FUSION system.

Similar set ups have been previously used in the ICU setting to achieve tight glucose control. In a study published in 2013,[71] the set up pictured below (Figure 22) was utilized, with the overall form factor being very similar to the FUSION system seen above (Figure 20).

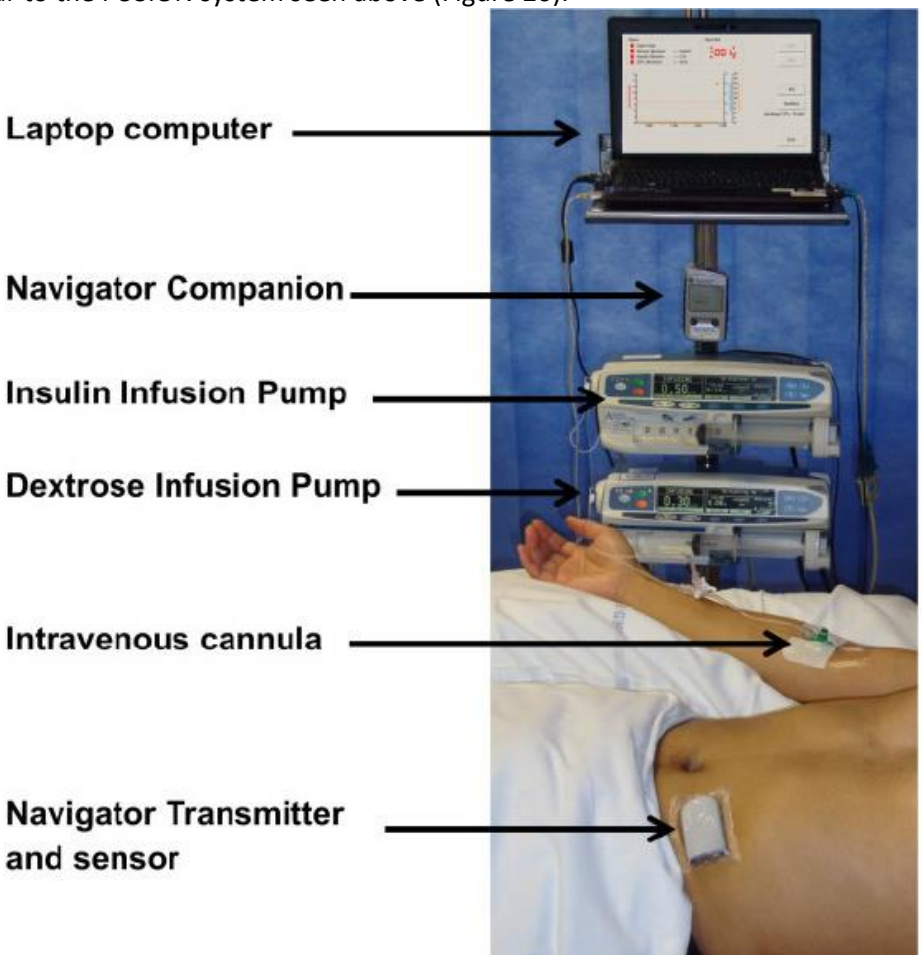


Figure 22 – Picture notes set up for fully functional closed loop glucose control system. System consists of a CGM placed in the abdominal position, a receiver for the CGM signal (Navigator Companion), a laptop housing the glucose control software, and two syringe pumps controlled by the MPC based glucose control software in the laptop. Leelarathna, Critical Care, 2013.

For this 48-hour study on 24 ICU patients the control range was 6-8 mmol/L. The closed loop patients had Reference Glucose Values measured on a blood gas machine every 30 minutes to 6 hours. The MPC based closed loop controller used in this study automatically adjusted the flows of insulin and/or 20% dextrose every 5 minutes based on the input from the CGM, the desired control range, and the MPC

controller. The control group patients were managed with a local insulin protocol and controlled to the same range. The results from this study are noted below (Table 10).

	Local Protocol (N=12)	Automated closed-loop (N=12)	p
Primary end point			
Time glucose in target (%) (6.0-8.0 mM)	18.5 (0.1-39.9)	54.3 (44.4-72.8)	0.001
Secondary end points			
Starting glucose (mM)	10.8 (9.9-12.0)	10.0 (8.9-11.1)	0.21
Mean glucose (mM)	9.1 (8.3-13.0)	7.9 (7.4-8.2)	0.001
Standard deviation of glucose (mM)	1.9 (0.8)	1.3 (0.5)	0.089
Time spent at glucose levels (%)			
4.0-10.0 mM	73.2 (21.2-89.4)	93.3 (86.5-100.0)	0.002
5.6-10.0 mM	73.2 (21.2-82.4)	92.2 (83.4-99.2)	0.001
>8.0 mM	78.4 (57.6-99.9)	39.0 (23.5-51.4)	0.001
>10.0 mM	26.8 (10.5-78.8)	6.7 (0-13.5)	0.002
<6.0 mM	0 (0-3.0)	4.6 (3.1-8.3)	0.028
<5.6 mM	0 (0-0)	0.7 (0-2.7)	0.128
<4.0 mM	0 (0-0)	0 (0-0)	NA
Hypoglycemia			
Episodes <4.0 mM	None	None	
Hypoglycemia treatments	None	None	
Hyperglycemia			
Number of subjects ≥ 15 mM	5 (42%)	1 (8%)	
Number of subjects ≥ 17 mM	4 (33.3%)	1 (8%)	
Episodes ≥ 15 mM	11	1	
Episodes ≥ 17 mM	13	1	
Insulin infusion-data			
Total units for 24 hours	40.9 (34.9-101.4)	57.4 (40.0-112.3)	0.478
Hourly infusion rate	1.7 (1.5-4.2)	2.4 (1.7-4.7)	0.478
Total dextrose infusion for 48 hours (g)	0.21 (0.0-5.2)	NA	NA
Data shown are mean (SD) or median (interquartile range).			

Table 10 – Data from study utilizing closed loop system shown above (Figure 22). Leelarathna, Critical Care, 2013.

Although the closed loop system in this study improved upon the results from the local protocol, it was only able to achieve a time in range 6-8 mmol/L of 54%, a time in range 3.9-8 mmol/L of 60%, and a CV of 16.5%. However, it did avoid any significant hypoglycemia.

Effective tight glucose control can decrease ICU mortality rates as has been previously reported. In addition, significant improvement in morbidity is expected, as demonstrated by the only large prospective tight glucose control study ever performed that achieved a high time in range while at the same time having no hypoglycemia. In this Japanese study of 447 pancreatic surgical patients,[72] the tight glucose control group (80-110 mg/dL) had an 86% time in range, while the intermediate control group (140-180 mg/dL) had a 97% time in range, with neither group experiencing any hypoglycemia. The tight glucose control group had a 58% reduction in the surgical site infection rate as can be seen below (Figure 23).

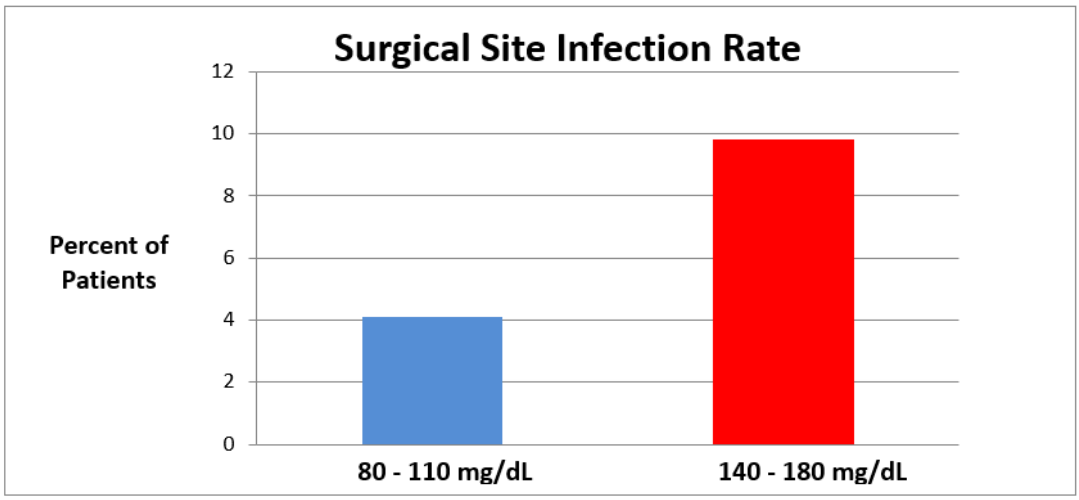


Figure 23 – Okabayashi, Diabetes Care, 2014.

A large study done at the John Hopkins Health System estimated that surgical site infections (SSI) cost their system around $21,000 per infection, or around $3.3 million annually.[73] There are around 150,000 SSI's per year in the U.S., thus tight glucose control in these patients has the potential to save around $1.8 billion per year.[74]

This same Japanese closed loop glucose control study also demonstrated a 21% reduction in the length of stay in the more tightly controlled group, as noted below (Figure 24).

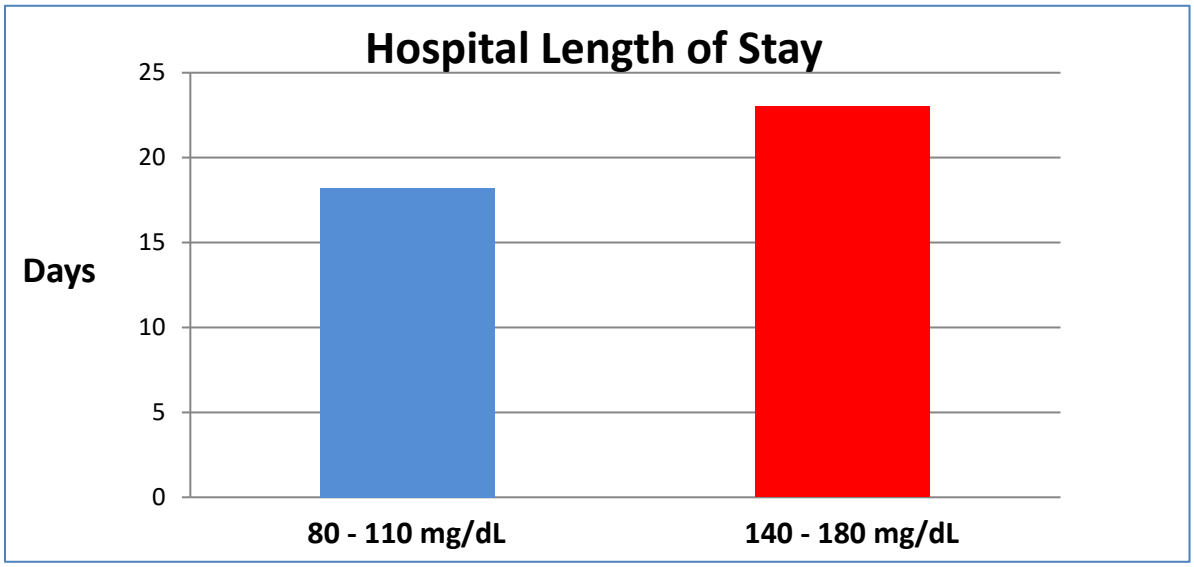


Figure 24 – Okabayashi, Diabetes Care, 2014.

Any intervention that shortens hospital length of stay will have a positive impact on reducing overall hospital cost of care, as the latter is directly correlated with length of stay.

To emphasize the size of the problem, in the U.S there are 80,000 ICU beds with 6 million annual admissions,[2] with the European Union experiencing similar numbers.[75] The U.S. spends 150 billion dollars caring for these ICU patients.[76] Given an average ICU mortality rate of 10%, an effective glucose control system that lowers ICU mortality rates by at least 20% would be expected to save 120,000 lives per year in the U.S. In addition, a safe and effective artificial pancreas system that reduces net cost of care by at least $1,000 per patient, if used on 50% of ICU patients, would be expected to reduce overall U.S. healthcare costs by 3 billion dollars annually. If the European Union were included, these numbers would be roughly doubled.

4 RISK/BENEFIT ASSESSMENT

4.1 KNOWN POTENTIAL RISKS

The main risk associated with tight glucose control studies is hypoglycemia, with hypoglycemia being defined as any glucose value less than 70 mg/dL. The rate of hypoglycemia has traditionally been close

to 20% in studies aiming at lower glycemic targets.[77,78] In addition, hypoglycemia in tight glucose control studies has been associated with increasing mortality rates,[14,18] although a causal relationship has not been established. The immediate risk of a hypoglycemic event, especially a clinically important one with glucose values less than 54 mg/dL, is impaired brain function resulting in a temporary coma, or a hypoglycemia induced seizure.[79,80] However, there does not appear to be any long term cognitive impairment in adults who have experienced hypoglycemic events.[81,82] An additional potential risk of tight glucose control is the development of hypokalemia, which can lead to a prolonged Qt interval and potentially fatal dysrhythmias. However, this issue has been reviewed and it was found that there was no association found between tight glucose control and development of prolonged Qt syndrome.[83,84]

Hypoglycemia is a risk for any tight glucose control study, however the AI based FUSION glucose control system under study was particularly effective at avoiding hypoglycemic events in the simulation and animal studies. When the control range was set to 100-140 mg/dL in the simulation studies, no glucose values less than 70 mg/dL were recorded in either study. In the two subject first in human study the percent time in range less than 70 mg/dL was zero.

The risks of severe hypoglycemia (< 54 mg/dL); moderate hypoglycemia (54 – 69 mg/dL) with associated hypoglycemia symptoms of anxiety, irritability, sweating, hunger, shakiness, fatigue, pale skin, lethargy, seizures; and symptoms of hypoglycemia at any level due to falling glucose levels (e.g., neuroglycopenia) will be mitigated by the following means:

1. Monitoring of the subject's glucose level with two Dexcom G6 CGM's.
2. Sharing of the Dexcom G6 CGM's values with study personnel via the Dexcom Follow App on two smartphones.
3. Setting the Dexcom CGM's to alarm for CGM glucose values less than 85 mg/dL.
4. Measurement of Reference Glucose Value for any CGM glucose value less than 85 mg/dL.
5. Measurement of Reference Glucose Values at a minimum frequency of every 1 hour.
6. Measurement of Reference Glucose Values every 10 minutes if either CGM has a glucose value less than 70 mg/dL.
7. Measurement of Reference Glucose Values every 10 minutes if the most recent Reference Glucose Value was less than 70 mg/dL.
8. Measurement of a Reference Glucose Value at any time if the subject displays any of the above noted signs of hypoglycemia.
9. Terminating the study on subject if the subject has a Reference Glucose Value less than 54 mg/dL.
10. Terminating the entire study if two subjects have a Reference Glucose Value less than 54 mg/dL.

For purposes of this document, the term Reference Glucose Value refers to the following:

1. A whole blood glucose value in mg/dL measured at the subject's bedside using the FDA approved Nova StatStrip Hospital Glucose Meter System. The whole blood sample should be immediately analyzed after it is taken from the subject.
2. The whole blood sample should be taken from the following two sources, which are listed in their order of preference:
    a. Venous blood sample from a retrograde hand vein intravenous catheter using the standard blood draw method of Emory University's CRC.
    b. Capillary blood sample from a fingerstick using the standard fingerstick method of Emory University's CRC.

If the subject experiences severe hypoglycemia as measured by a Reference Glucose Value, moderate hypoglycemia as measured by a Reference Glucose Value with hypoglycemia symptoms, or neuroglycopenia, they will receive the following treatments to minimize their risks:

1. The subjects will be given free access to snacks and glucose containing juices of sufficient quantity to raise their Reference Glucose Value so that it is greater than 70 mg/dL and so that they are no longer experiencing any symptoms of hypoglycemia.
2. The subjects will be given a rescue dose of 15 mL of 50% dextrose in any of the following scenarios:
    a. For a Reference Glucose Value less than 54 mg/dL.
    b. For a Reference Glucose Value of 54-69 mg/dL with accompanying symptoms of hypoglycemia – anxiety, irritability, sweating, hunger, shakiness, fatigue, pale skin, lethargy, seizures.
    c. For any Reference Glucose Value when the subject is experiencing signs of hypoglycemia caused by a rapid fall in the subject's blood glucose level (e.g., neuroglycopenia) and the ingestion of snacks or glucose containing juices do not relieve these symptoms within 10 minutes from the time the snacks/juice is ingested.
3. If intravenous access is no longer available and the subject has a Reference Glucose Value less than 70 mg/dL, or is exhibiting signs of neuroglycopenia, the subject will be given Glucagon 1 mg intramuscularly every 15 minutes as needed until their Reference Glucose Value is greater than 70 mg/dL on two consecutive checks that are separated in time by at least 30 minutes, and when their hypoglycemia symptoms have completely resolved.

The other potential risks of participating in this study include severe hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, excessive blood removal (lab draws), and fluid overload.

Given the FUSION systems results in its first in human testing, the current studies proposed control range of 100-140 mg/dL, and the above monitoring and risk mitigation strategies, no alternative procedures are warranted at this time.

4.2 KNOWN POTENTIAL BENEFITS

The immediate benefits for participants with diabetes in a brief (31 hour) tight glucose control study in a CRC setting are limited. However, development of a closed loop glucose control system designed for use in the inpatient setting may have long term benefits for this patient population, as preliminary studies have demonstrated improved outcomes through use of automated closed loop glucose control in this group in the non-ICU inpatient setting.[85,86]

With regards to benefits to ICU patients, as has been previously noted, effective tight glucose control can lead to decreased morbidity rates, whether it be decreased wound infection rates in post-operative patients,[72] or decreased renal failure and blood transfusions rates.[6] In addition, mortality rates will be lower if the subject is able to maintain a high time in the control range,[16] while at the same time avoiding any hypoglycemia events.[14] Finally, safe and effective tight glucose control has the potential to lower critical illness related mortality including COVID-19 related mortality .[35]

Long term potential benefits for the ICU patient population mainly relate to a shorter overall recovery period based on decreased complication rates and the potential for a shorter ICU length of stay to decrease mortality rates after hospital discharge.[87]

4.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

4.3.1 FAILURE OF DEXCOM G6 CONTINUOUS GLUCOSE MONITOR(S)

The risk of complete failure of the continuous glucose monitoring system will be mitigated through use of two Dexcom G6 CGM systems, which will provide redundancy to this critical component of the FUSION artificial pancreas system. In addition, replacement of the Dexcom CGM system – sensor, transmitter, or receiver – will be allowed if any of these three components of an individual CGM system experiences a failure. To clarify, the FUSION system uses a simple average of the two Dexcom G6 CGM values to decide what steps to take to bring the subject's blood glucose value into the desired control range. In order to be averaged, these two Dexcom G6 CGM values must be time stamped within 5 minutes of each other. The FUSION system will operate for up to four hours with glucose readings from only one Dexcom G6 CGM system, and for up to 20 minutes with no values from either Dexcom G6 CGM

system. The FUSION system will automatically shut down after four hours if it has only one Dexcom G6 CGM system available for use. The FUSION system will automatically shut down if it has no Dexcom G6 CGM systems available for use for a period of time exceeding 20 minutes.

The Dexcom G6 CGM Sensor/Transmitter pair communicate via Bluetooth, to the Dexcom G6 Receiver. IMT has not altered in any way, how the Dexcom G6 CGM system works or handles communications between the Transmitter and Receiver. The Dexcom G6 CGM system sends new glucose values to the Receiver every 5 minutes, if they are available, from the Sensor/Transmitter pair attached to the subject. The Dexcom G6 CGM manual notes that the Transmitter and Receiver must be within 20 feet of each other, with no obstacles between them (e.g., walls) in order to effectively communicate via Bluetooth. The FDA is aware of the 20 foot range limitation of the Dexcom G6 CGM system and has approved this CGM system for use in artificial pancreas systems. IMT has developed software called a Driver, that queries the database of the Dexcom G6 Receiver, every 30 seconds, for new glucose values. When the Driver discovers new date/time stamped glucose values in the database of the Receiver, it brings these values into a glucose queue within the FUSION system for use by the FUSION system. The FUSION system will only average glucose values that are time stamped within 5 minutes of each other. The all-in-one Medical Computer running the FUSION systems software is connected to the Dexcom G6 CGM Receiver via a serial data cable. In our internal testing, each Dexcom G6 CGM Receiver was able to receive new glucose values from the Dexcom G6 Transmitter 99.53% of the time within the designed 5 minute time interval.

The benefit of using the Dexcom G6 CGM is that the FDA has already approved this system for use as an integrated continuous glucose monitor (iCGM) in automated insulin dosing (AID) systems for use in treatment of patients with diabetes in the outpatient setting. This study and follow-up studies to be performed in the ICU setting will attempt to demonstrate the feasibility of using the Dexcom G6 CGM system in an AID system (e.g., FUSION) designed for use in the inpatient setting.

In addition, the study will also demonstrate the ability of the Dexcom G6 transmitter to simultaneously transmit its glucose data to one medical device (e.g., the Dexcom G6 Receiver) and the Dexcom G6 Follow App on a mobile phone placed 15 feet from the subject's bed. Demonstration of this functionality is important, as a mobile phone device will be needed in the ICU setting to provide remote monitoring (e.g., outside of the room) of the subject's continuous glucose measurements.

4.3.2 USE OF INNACURATE CGM GLUCOSE VALUE FOR GLUCOSE CONTROL

The risk of using an inaccurate CGM value for glucose control will be mitigated by averaging the glucose value of the two CGM devices. In addition, **independent Reference Glucose Values (Nova StatStrip Hospital Glucose Meter System) will be obtained every 10-60 minutes to ensure subject safety.**

The benefit of using Dexcom's G6 CGM, which has already been approved as an iCGM, is to determine its accuracy in different scenarios/settings (e.g., participants with diabetes in the proposed study; COVID-19 patients in ICU in future study).

The benefit of obtaining Reference Glucose Values every 10-60 minutes is to independently monitor for hypoglycemia in cases where the CGM systems are providing the FUSION system with false high glucose levels that could lead to hypoglycemia, or to monitor for hyperglycemia in cases where the CGM systems are providing the FUSION system with false low glucose levels that could lead to hyperglycemia. The Reference Glucose Values can be used to administer rescue doses of 50% intravenous dextrose in cases of severe hypoglycemia (< 54 mg/dL), moderate hypoglycemia (54-69 mg/dL) with associated hypoglycemia symptoms, or in cases of neuroglycopenia.

4.3.3 USE OF FALSE LOW CGM VALUES DUE TO COMPRESSION OF SENSOR SITE

The risk of using a CGM value that is falsely low due to local compression of the sensor site, due to the subject laying on the sensor site, will be mitigated by monitoring of the Dexcom G6 CGM values by the study nurse. When the study nurse notes the presence of a compression artifact, which manifests as a sudden non-physiologic fall in the glucose value (e.g., < ± 2 mg/dL/min), the study nurse will move the subject until they are no longer laying on the sensor site. If one of the two abdominal sensors experiences repeated compression artifact values, the study nurse will have the option of placing a new CGM sensor on an alternative abdominal site, or on the posterior aspect of the contralateral upper arm from the abdominal sensor that continues to function normally (e.g., right side of abdomen and posterior aspect of left upper arm). The arm position may decrease the risk of both sensors suffering from compression artifacts, which could occur if the subject were to lay on both of their abdominal sensors during sleep.

A recent study involving the Dexcom G7 CGM revealed that positioning the CGM on the back of the upper arm was as accurate and reliable as the abdominal position.[88] This study, which involved 316 participants and 77,774 paired (CGM vs YSI) glucose values, demonstrated an overall MARD of 8.2% for the arm and 9.1% for the abdomen. Among the 308 sensors worn on the arm, 291 (94.5%) had >80% of CGM-YSI matched pairs that met the %20/20 accuracy criterion. Among the 311 sensors worn on the abdomen, 272 (87.5%) had >80% of matched pairs that met the %20/20 accuracy criterion. There were no serious adverse events in the study population.

The benefit of using the arm position will be to demonstrate its potential utility in a closed loop glucose control system, and to demonstrate its accuracy relative to the abdominal position as measured against the Reference Glucose Value.

4.3.4 EXCESSIVE VOLUME LOADING FROM FUSION SYSTEM

In the first in human study performed on two subjects with type 2 diabetes in the CRC, the FUSION system infused an average of 26% of the subject's total daily volume needs during the 24 hour study period. The risks to the subjects from this amount of volume include generalized edema in the setting of abnormal renal/liver function, or exacerbation of underlying congestive heart failure in the setting of underlying congestive heart failure. This risk will be mitigated by selecting subjects who have no underlying renal, liver, or cardiac conditions.

This risk will also be mitigated by further optimizing the FUSION systems glucose control software, based on an analysis of the results from the first two subjects studied. These optimization efforts include steps to prevent excessive use of insulin during states of hyperglycemia (e.g., > 140 mg/dL), which can lead to a rapid fall of elevated glucose values into and through the desired glucose control range of 100-140 mg/dL. This rapid fall of glucose levels leads the FUSION system to either start a dextrose infusion if one is not currently infusing, or to rapidly increase the rate of the current dextrose infusion. The FUSION systems glucose control software will also be optimized to decrease the dextrose infusion more quickly in states where the glucose level is in the desired control range and is either stable or increasing. These efforts to avoid excessive use of dextrose should decrease overall fluid intake, as the dextrose infusion accounted for 88% of the total fluid given by the FUSION system.

Finally, the risk of fluid overload will be minimized through routine monitoring of the subjects for signs of fluid overload, throughout the 24-hour closed loop glucose control session. These signs will include evidence of peripheral edema (swollen hands, ankles, legs, eyelids), increased respiratory rate, shortness of breath, or signs of pulmonary edema on exam such as rales. Excessive volume loading, from the FUSION system, will be defined as fluid delivered by the FUSION system (e.g., insulin infusion and dextrose infusion) in excess of 2000 mL during the 24 hour closed loop session. If this fluid delivery threshold is exceeded on a subject, the study will be stopped on that subject.

The benefits of creating a closed loop glucose control system for use in the inpatient setting outweigh the risks of excessive fluid intake in this highly monitored CRC study.

4.3.5 FAILURE OF ABILITY TO OBTAIN A REFERENCE GLUCOSE SAMPLE

This risk will be minimized through use of two sample sites for Reference Glucose Values. The preferred sample site will be a retrograde hand vein intravenous catheter. If the clinical study staff is unable to obtain a venous draw from the retrograde hand vein catheter for any reason, they will obtain a capillary blood sample from a fingerstick. To be clear, if the retrograde hand vein catheter is no longer available as a sample site, the 24-hour closed loop glucose control study may be completed using fingerstick capillary samples as a source for Reference Glucose Values.

4.3.6 FAILURE OF REFERENCE GLUCOSE ANALYZER

In cases where there is no Reference Glucose Value available for a period exceeding 60 minutes, the risk will be mitigated through termination of the study on that subject. An additional risk of relying on reference glucose analyzers is that they may produce inaccurate independent glucose results. This risk will be minimized through use of the Nova StatStrip Hospital Glucose Meter System, which the FDA has approved for use in the ICU setting.

4.3.7 FAILURE OF CONTROL ALGORITHM TO PERFORM AS EXPECTED

The risk of the control software to not perform as expected has been mitigated through version control of the software. In addition, the rules and sequencing of the software have been independently verified by the both the designer of the software, and the software developer. Furthermore, the control software to be used in this study has been tested in two simulation studies, two animal studies, and a first in human study with no instances of software failure, and excellent overall glucose control capabilities as demonstrated by the previously mentioned results. Finally, the glucose control software has undergone an independent verification and validation process by an outside company (JKI) that specializes in working with the LabVIEW engineering software suite used to create the FUSION systems glucose control software. This verification and validation testing is repeated with each new version of the software, and prior to using the updated software in the clinical setting. The risks of software failure will be mitigated through independent monitoring of the subject's glucose values to prevent the serious risk of hypoglycemia. Complete software failure during the study would lead to termination of the study.

The benefit of using closed loop glucose control software is demonstration of the feasibility of using this software to create a complete glucose control system and outweighs the noted risks.

4.3.8 FAILURE OF SYRINGE PUMPS TO ACCURATELY DELIVER DOSES OF INTRAVENOUS INSULIN AND DEXTROSE

The risk of the syringe pumps to not accurately deliver doses of insulin and dextrose has been mitigated through assessment of their accuracy prior to the study using a balance scale technique.[89] This testing has demonstrated the accuracy of the syringe pumps to be within ± 5% from the prescribed infusion rate/volume. In addition, the infusion pump output rates are monitored by the glucose control software every 10 seconds to ensure the pump output rates match the prescribed rates from the software. If these rate differences are greater than 20%, the study is temporarily stopped until the syringe pump is replaced.

The benefits of using the KDS Legato 100 syringe pumps is that they were designed to work with the LabVIEW software that was used to implement the glucose controller, have a demonstrated infusion rate accuracy of within ± 5%, and can detect intravenous line occlusion and alert the clinician to this condition (e.g., occlusion) if it is detected.

4.3.9 RISK OF IMPROPER SYRINGE PUMP SET UP

The risk of the study personnel to not properly set up and use the syringe pumps will be mitigated through pre-study tutorials on their use, in addition to making available a standard operating procedure (SOP) as to their original set up and ongoing use. In addition, an IMT representatives will be immediately available for consultation throughout the entirety of the 24 hours of closed loop glucose on each subject.

The benefit of using the KDS Legato 100 syringe pumps is their highly accurate dosing and their compatibility with the LabVIEW software used to develop the FUSION closed loop glucose control system being tested in this study. It is expected that the KDS Legato 100 syringe pumps will not be part of the final FUSION system for which marketing approval will be sought.

4.3.10 RISK OF DIABETIC KETOACIDOSIS (DKA)

DKA is a metabolic condition brought on by lack of sufficient insulin supply such that the body can no longer use glucose as a fuel source, which leads to excessive breakdown of fat, and abnormal labs consisting of elevated blood levels of glucose and beta hydroxybutyrate, with a concomitant lowering of the blood pH. The risk of the participants entering the study while they are in DKA will be mitigated by screening for ketones at the time they are admitted to the CRC on visit 3. This screening will include a capillary blood Reference Glucose Value measured on the Nova StatStrip Hospital Glucose Meter System and blood ketone levels measured on the Nova Max Plus ketone meter (Nova Biomedical).

The risk of the subjects developing DKA while they are in the study will be mitigated by obtaining Reference Glucose Values at least every 1 hour. If the subjects CGM or Reference Glucose Value is > 240 mg/dL, the subjects will have their blood screened for ketones using the Nova Max Plus ketone meter. If the subject's blood ketone level is > 1 mmol/L, they will have venous blood sent for a basic metabolic panel, pH, and beta hydroxybutyrate to determine if they are in DKA. Subjects who are found to be in DKA, during their stay in the CRC during visit 3, will be removed from the study.

The benefit of testing the FUSION system on type 1 and type 2 diabetic subjects, whose blood glucose levels are difficult to control, outweighs the risk of the subjects developing DKA, given the information on the FUSION systems performance that will be gathered during the course of this study.

4.3.11 RISK OF SEVERE HYPERGLYCEMIA

Severe hyperglycemia is defined as a Reference Glucose Value greater than 240 mg/dL. In subjects with type 1 or type 2 diabetes, this degree of hyperglycemia may be a sign that the subject is at risk of developing DKA or hyperosmolar hyperglycemic syndrome (HHS). The risk of subjects developing untreated severe hyperglycemia while they are in the study will be mitigated by monitoring of the subject's Reference Glucose Values at least every 1 hour with the Nova StatStrip Hospital Glucose Meter. CGM alarms will be set up to alert the research nurse and study staff for CGM glucose values > 240 mg/dL for early detection of up trending glucose values. If the subject has a CGM or Reference Glucose Value greater than 240 mg/dL, the risk of DKA will be further mitigated by monitoring the subjects Reference Glucose Values every 30 minutes until their Reference Glucose Value is less than 240 mg/dL. The risk of DKA will be mitigated by terminating the study if a subjects' Reference Glucose Value remains > 240 mg/dL for more than 2 hours.

4.3.12 RISK OF HYPEROSMOLAR HYPERGLYCEMIC SYNDROME

HHS is defined as a serious complication in subjects with type 2 diabetes, and occasionally in subjects with type 1 diabetes, that occurs when the subject experiences severe hyperglycemia (usually >600 mg/dL) for a prolonged period of time. HHS may produce severe dehydration, altered level of consciousness, and coma. The risk of subjects developing HHS while they are in the study is expected to be low and will be mitigated close monitoring of the subject's Reference Glucose Values at least every 1 hour with the Nova StatStrip Hospital Glucose Meter. If the subject has a CGM value greater than 240 mg/dL (detected by CGM alarm set for glucose values > 240 mg/dL) or Reference Glucose Value greater than 240 mg/dL, the risk will be further mitigated by monitoring the subjects Reference Glucose Value every 30 minutes until their Reference Glucose Value is less than 240 mg/dL. Finally, the risk will be mitigated by terminating the study if the subjects CGM or Reference Glucose Value remains > 300 mg/dL for more than 1 hour.

The overall risks of the study are outweighed by the potential benefit of demonstrating the safety of the FUSION systems AI based glucose control software, which is the first step in testing this software with an eventual goal of using it to create a closed loop glucose control system for use in the ICU setting.

5 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
i. Safety To assess the hypothesis that an AI based glucose controller will provide safe glucose control in participants with type 2 diabetes consuming three meals over the course of the 24-hour closed loop glucose control session.	The percent of all glucose values that are in the hypoglycemic range, when the latter is defined as glucose values less than 70 mg/dL.	Avoidance of hypoglycemia during tight glucose control leads to decreased mortality rates, and thus measurements of the rate of occurrence of hypoglycemia can be considered an assessment of the overall safety of the glucose control system under study.
2. Efficacy To assess the hypothesis that an AI based glucose controller will provide effective glucose control in participants with type 2 diabetes consuming three meals over the course of the 24-hour closed loop glucose control session.	The percent of all glucose values that are within the range of 70-180 mg/dL.	ICU mortality rates increase when patients experience both hypoglycemia (< 70 mg/dL) and hyperglycemia (> 180 mg/dL). Thus, testing the ability of the AI based glucose control system to maintain the study subjects in the range of 70-180 mg/dL will give an indication of its ability to avoid these two deleterious glycemic states.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
The secondary objectives of the study are to assess the controller's ability to minimize glucose curve measurements associated with increased ICU morbidity/mortality rates, and to maximize those measurements associated with decreased ICU morbidity/mortality rates.	1. Measure the percent of glucose values that are within the severe hypoglycemic range of 0 – < 54 mg/dL. 2. Measure the percent of glucose values that are within the moderate hypoglycemic range of 54-69 mg/dL. 3. Number of hypoglycemic (< 70 mg/dL) events. Each event separated by at least one glucose value >= 70 mg/dL. 4. Measure the percent of all glucose values that are within the desired glucose control range of 100 – 140 mg/dL. 5. Measure the percent of glucose values that are within the range of 70-140 mg/dL. 6. Measure the percent of glucose values that are within the hyperglycemic range of > 140 mg/dL. 7. Measure the percent of glucose values that are within the range of 70-180 mg/dL. 8. Measure the percent of glucose values that are within the hyperglycemic range of > 180 mg/dL. 9. Mean glucose level (mg/dL). 10. Measure of dispersion – coefficient of variation. 11. The study data will be used to determine the percentage of the Dexcom's G6 CGM's glucose values in each zone using a Clarke error grid analysis.[1] This same calculation will be performed on the average of the two Dexcom	The chosen secondary endpoints are routinely measured in glucose control studies and serve to provide a more complete picture of the AI based glucose control systems ability to both safely and effectively provide glucose control.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	G6 CGM systems used by the FUSION system for purposes of glucose control.	
Tertiary/Exploratory		
None planned		

The glucose data for the above statistical analysis will be the glucose data used by the FUSION system for purposes of glucose control, unless otherwise specified.

6 STUDY DESIGN

6.1 OVERALL DESIGN

Tight glucose control in the ICU setting is difficult to achieve. We hypothesize that a closed loop glucose control system based on artificial intelligence will improve upon the glucose control currently achieved by open loop systems. This non-randomized Early Feasibility First in Human Study at a single study site will test the ability of a prototype closed loop glucose control system to provide safe and effective glucose control in participants with type 1 diabetes who lack endogenous insulin production, and type 2 diabetes who have insulin resistance profiles that match those of ICU patients.[58] The study will be performed in a CRC setting on two participants with type 1 diabetes and six participants with type 2 diabetes over a time period of thirty-two hours per subject. The subjects will all consume three standardized meals during the 24-hour period their blood glucose levels are being controlled by the FUSION system. Study volunteers will be recruited from the adult endocrinology clinics of Emory University and/or Grady Hospital in Atlanta. Identified subjects who have been screened and enrolled in the study will have the study completed within two weeks of enrollment. An interim data analysis is not planned.

6.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A non-randomized Early Feasibility Study design was chosen as this represents a first in human test of this artificial intelligence based closed loop glucose control system. The main goal of the study will be to test the safety and efficacy of the FUSION closed loop glucose control system, as measured by the percent of glucose values less than 70 mg/dL (safety), and the percent of glucose values in the range of 70-180 mg/dL (efficacy). Testing in the CRC setting was chosen as it is a highly monitored environment, and the subjects can be carefully chosen based on inclusion/exclusion criteria.

6.3 JUSTIFICATION FOR DOSE

For safety reasons the maximal allowed insulin dose (e.g., NovoLog) will be 0.5 units/kg/hour and the maximal dextrose (D10NS) infusion rate will be 4 mL/kg/hour, except during periods of dextrose boluses, when the maximal infusion rate will be 6.25 mL/kg/hour over a 5-minute period. These limits are consistent with a similar prior study.[71]

6.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

7 STUDY POPULATION

7.1 INCLUSION CRITERIA

A. Participants with type 1 and type 2 diabetes are eligible to be included in the study only if they meet all the following criteria:

1. Are 18-70 years of age, inclusive.
2. Can understand and sign an informed consent, communicate with the investigator, and understand and comply with the protocol requirements.
3. Have had a diagnosis of type 1 or type 2 diabetes for a period of at least 1 year.
4. Use insulin injections at home for glucose control and are on a stable insulin regimen without more than a 20% change in their total daily insulin dose during the previous 3 months. Their total daily insulin dose during the previous 3 months will be confirmed through a review of the subject's electronic health record, insulin prescriptions, and insulin pump settings (if applicable).

5. Have a hemoglobin A1c (HbA1c) in the range of 7.0 – 10.0%.
6. Have a hemoglobin in the normal range for sex:
    a. Females: 12-15.5 grams/dL.
    b. Males: 13.5–17.5 grams/dl.
7. Have adequate venous access sites in upper extremities.
8. Body weight between 40 – 150 kg.

7.2 EXCLUSION CRITERIA

A. Subjects will be excluded from the study if they meet any of the following criteria:

1. Have participated in an interventional medical, surgical, or pharmaceutical study within 30 days of screening.
2. Have a known hypersensitivity to any of the components of study treatment.
3. Have skin disease/injury at Dexcom G6 CGM insertion site(s) that would prevent insertion of the CGM.
4. Currently abuses drugs or alcohol or has a history of abuse that in the investigator's opinion would cause the individual to be noncompliant.
5. Have a medical condition that in the opinion of the investigator could affect study participation and/or personal well-being.
6. Have a clinically significant history or presence of any of the following conditions:
    a. Hepatic failure or has alanine aminotransferase (ALT) greater than 3 times the upper limit of normal.
    b. Has an estimated GFR <60 ml/min/1.73 m^2 or End Stage Kidney Disease on renal replacement therapy.
    c. Type 2 diabetic subjects who have a C-peptide level less than 0.2 nmol/L (these subjects will be referred to their primary care doctor or endocrinologist for further work up).
    d. Have congestive heart failure of class 1 or greater on the NYHA classification system.
    e. Have a history of seizures.
    f. Have a history of cerebrovascular accident.

g. Have a history of ischemic heart disease.

7. For female subjects of potential childbearing age (age 18 to 55) they will be excluded if:
    a. Pregnant.
    b. Refuse to agree to a pregnancy test at the time of enrollment.
    c. Have a positive urine pregnancy test at the time of enrollment.
8. Have a positive COVID-19 test within 14 days of visit 3.
9. Have any COVID-19 related symptoms in the 14-day period prior to visit 3.
10. Have a known unprotected COVID-19 exposure in the 14-day period prior to visit 3.

7.3 LIFESTYLE CONSIDERATIONS

Not applicable.

7.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a failure to meet all inclusion and exclusion criteria will not be rescreened for participation in the trial.

7.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants with type1 and type 2 diabetes will be recruited from the Diabetes Center at Grady Hospital and adult endocrinology clinics at Emory Healthcare, located in Atlanta, Georgia. All adult type 1 and type 2 diabetic patients being cared for in these clinics will be screened for inclusion in the study. The original screening will include age, weight, length of diagnosis of diabetes, use of insulin in the home setting, and their most recent HbA1c level. Potential subjects who pass these criteria will then be assessed for exclusion criteria. Potential subjects who pass the exclusion criteria will be approached for participation in the study. Willing participants will be scheduled for enrollment during visit 2. Subjects

who sign an informed consent during visit 2 will have blood drawn to evaluate their hemoglobin, HbA1c, ALT, creatinine, and C-peptide (type 2 diabetic subjects) levels. Female subjects aged 18-55 inclusive who have signed an informed consent will also have a urine pregnancy test performed during visit 2. It is anticipated that 500 adult type 1 and type 2 diabetic subjects will need to be screened to yield 8 subjects for participation in the study. It is expected that the inclusion criteria will eliminate 97% of potential enrollees. It is expected that the exclusion criteria will eliminate another 30% of the remaining potential enrollees. Study participants will be compensated for participation in the study.

8 STUDY INTERVENTION

8.1 STUDY INTERVENTION(S) ADMINISTRATION

8.1.1 STUDY INTERVENTION DESCRIPTION

8.1.1.1 COMPONENTS OF CLOSED LOOP GLUCOSE CONTROL SYSTEM

1. Two complete Dexcom G6 continuous glucose monitoring systems – Glucose sensor, Transmitter, and Receiver
2. Two mobile phones with the Dexcom G6 Follow App
3. One Medical Computer and associated power cord
4. One Powered Medical Cart and associated power cord
5. Two KDS Legato 100 syringe pumps and associated power cords
6. Two serial data cables to attach syringe pumps to Medical Computer
7. Two serial data cables to attach Dexcom G6 Receivers to Medical Computer

8.1.1.2 VISIT 1, SCREENING

This screening visit includes evaluating the medical history, comprising preexisting conditions and concomitant medications of type 1 and type 2 diabetic subjects being seen at the Diabetes Center at Grady Hospital and the adult endocrinology clinics of Emory Healthcare, located in Atlanta, Georgia. Those subjects who meet study inclusion criteria, and who do not meet any study exclusion criteria, will be approached for participation in the study. Willing participants will be scheduled for visit 2, for purposes of obtaining an informed consent and enrolling them in the study.

8.1.1.3 VISIT 2, ENROLLMENT

Subjects who volunteer for the study will have the study thoroughly explained to them during visit 2. Subjects who willingly volunteer for the study, after having all their questions answered, will sign an informed consent. Subjects who have signed an informed consent will be assigned a unique identification number that will remain the same throughout the study. Those subjects who have signed an informed consent and whose lab results obtained during visit 2 do not exclude them from the study, will proceed to visit 3, which must occur within 2 weeks of the date of enrollment. The following instructions will be given to the subjects in preparation for visit 3:

1. For subjects taking the SGLT-2 inhibitor Ertugliflozin, they will be instructed to stop taking this medication four days prior to visit 3.
2. For subjects taking the SGLT-2 inhibitors Canagliflozin, Dapagliflozin, and Empagliflozin, they will be instructed to stop taking these medications three days prior to visit 3.
3. For subjects taking sulfonylureas or meglitinides, they will be instructed to stop taking these medications after their morning doses on the day prior to visit 3 (e.g., if visit 3 starts on a Wednesday, the subjects will stop taking these medications after their morning doses on the previous day = Tuesday).
4. If usually taking long-acting insulin in the PM, then on the evening prior to visit 3:
   a) Take half the usual evening dose of long-acting insulin if history of nocturnal hypoglycemia.
   b) Take the full usual dose of insulin if no history of nocturnal hypoglycemia.
   c) Insulin doses may also be adjusted at the discretion of the investigators (endocrinologists: Dr Francisco Pasquel and Dr. Georgia Davis).
5. Subjects to fast after midnight on the evening prior to visit 3.
6. Subjects to not take any oral anti-hyperglycemic medications on the morning of visit 3.
7. After admission to the CRC on the morning of visit 3, all Reference Glucose Values and insulin administration will be performed by the clinical study staff of the CRC. Insulin dosing will be at the recommendation of adult endocrinologists (Drs. Pasquel or Davis) who are the principal investigators for this study. The dose of short acting insulin ordered after admission to the CRC will be based on the amount of carbohydrates ingested by the subjects for breakfast after their CRC admission, their Reference Glucose Value measured just prior to breakfast, and their usual home routine.

8.1.1.4 VISIT 3, TIME 0 TO 5 HOURS (PREPARATION FOR CLOSED LOOP GLUCOSE CONTROL STUDY)

1. **General**

All subjects will be admitted between the hours of 0600 to 0700 to a single patient CRC room large enough to hold the subject, study personnel and necessary equipment. The study equipment, at a

minimum should include a cardiac monitor, pulse oximeter, intermittent blood pressure capabilities, and a resuscitation cart.

2. Screening Prior to Initiation of the Closed Loop Glucose Control Session

The subjects will be tested for the presence of diabetic ketoacidosis and appropriate Reference Glucose Values prior to proceeding to steps 3-6 below. This testing will include:

i. Reference Glucose Value at time of admission to the CRC – If the Reference Glucose Value is greater than 300 mg/dL, the subject will be screened for blood ketones using the Nova Max Plus (Nova Biomedical) ketone meter. If the Reference Glucose Value is less than 70 mg/dL or the subjects are experiencing any symptoms of hypoglycemia, regardless of their Reference Glucose Value, the subjects will be offered a snack or glucose containing juice. To be clear, the Nova Max Plus ketone meter will be used for any blood ketone analysis performed during the time the subjects are in the CRC.

ii. Blood ketones – The study will be cancelled if the blood ketones are > 1 mmol/L. If blood ketones are > 1 mmol/L, a venous blood sample will be sent to the central lab at Emory University for a basic metabolic panel, venous pH and beta-hydroxybutyrate to rule out diabetic ketoacidosis. If diabetic ketoacidosis is confirmed, the subject will be stabilized per the usual routine care at Emory Healthcare.

iii. Blood glucose prior to insertion of Dexcom G6 CGM's and intravenous lines – The subjects Reference Glucose Value must be in the range of 70-300 mg/dL prior to insertion of the two Dexcom G6 CGM's and two intravenous lines.

In addition, the closed loop glucose control session of the study will not be initiated if the participant has symptoms requiring action (e.g., abdominal pain, vomiting, unable to eat or drink, fever ≥ 101.5), regardless of blood glucose or ketone levels.

3. Dexcom G6 CGM devices

The subjects will have two Dexcom G6 CGM devices placed in the abdominal position, approximately 5 cm to the left or right of the umbilicus (Figure 25).

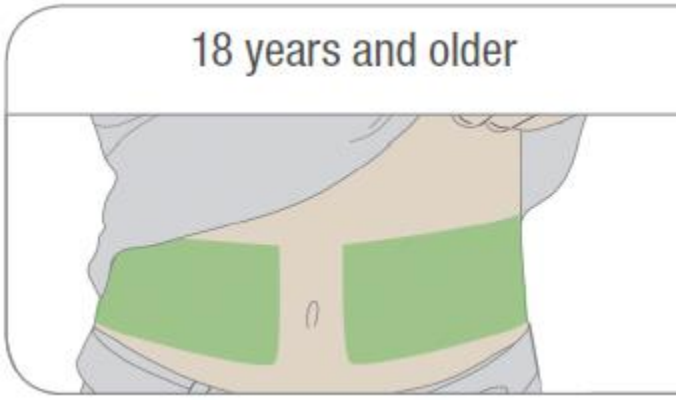


Figure 25 – Green shaded areas denote appropriate areas of the abdominal wall to place the Dexcom G6 CGM's. This figure is from the Dexcom G6 CGM user manual.

The CGM devices should be placed shortly after arrival to the CRC facility. For the Dexcom G6 CGM labeled "#1", enter the glucose sensors four-digit code and the transmitters six-digit serial number into the Dexcom G6 Receiver labeled "#1" and into the Dexcom G6 Follow App on the mobile phone labeled "#1". For the Dexcom G6 CGM labeled "#2", enter the glucose sensors four-digit code and the transmitters six-digit serial number into the Dexcom G6 Receiver labeled "#2" and into the Dexcom G6 Follow App on the mobile phone labeled "#2". Position the mobile phones 15-20 feet from the bed the subject will be using during the study.

4. Peripheral Intravenous Lines

For purposes of medication infusion, all subjects will have a peripheral IV placed into the antecubital vein of one arm. For purposes of blood removal, all subjects will have an IV placed in the contralateral hand in a retrograde position. The hand with the retrograde IV will be warmed to 50-55 degrees Celsius with a commercial warming box or warming pad for purposes of arterializing the venous blood.[90]

5. Reference Glucose Value

After both Dexcom CGM's have started to return glucose values to the Dexcom Receivers, and prior to starting the closed loop glucose control portion of study, a Reference Glucose Value(s) (taken from arterialized retrograde hand IV line) will be measured using the Nova StatStrip Hospital Glucose Meter System. If the retrograde hand vein is no longer available at any point during visit 3, Reference Glucose Values may be obtained from a finger stick (capillary blood), with analysis of this sample being performed on the Nova StatStrip Hospital Glucose Meter System.

On July 12, 2018, the FDA cleared the Nova StatStrip Hospital Glucose Meter System for point of care capillary blood glucose monitoring for all hospital patients, specifically including those receiving intensive medical intervention therapy. According to the FDA's 510(k) Substantial Equivalence Determination Decision Summary Assay and Instrument Combination Template for this product, two

studies were performed. In the first study for blood glucose values less than 75 mg/dL, 1 of 1 specimen (100%) was compliant, and for blood glucose values greater than or equal to 75 mg/dL, 484/567 (85.4%) specimens were compliant. In the second study for blood glucose values less than 75 mg/dL, 1614/1894 (85.2%) specimens were compliant, and for blood glucose values greater than or equal to 75 mg/dL, 12799/14884 (86.0%) specimens were compliant.[91]

The Nova StatStrip Hospital Glucose Meter System has been cleared for use on arterial, venous, and capillary whole blood samples, and is currently used to guide intravenous insulin infusion rates in the ICU setting.

6. Calibration of Dexcom G6 CGM's

The Dexcom G6 CGM's will be calibrated under the following scenarios:

1. The Dexcom G6 CGM value(s) do not meet CGM Validation Criteria
   If one or both of the Dexcom G6 CGM's are more than 20 mg/dL different from the Reference Glucose Value for CGM values less than 100 mg/dL, or are more than 20% different from the Reference Glucose Value for CGM values greater than or equal to 100 mg/dL at any time during visit 3, they will be recalibrated against the result from the Reference Glucose Value (using the Dexcom G6 receiver(s)). This calibration must occur within 5 minutes of obtaining the Reference Glucose Value sample. If the Dexcom G6 Receivers are recalibrated, the matching mobile phone's Dexcom App must also be recalibrated at the same time (e.g., if Dexcom Receiver #1 is recalibrated, also recalibrate the Dexcom G6 Follow App in mobile phone #1). If a Dexcom G6 sensor is recalibrated, a follow up CGM one hour after the recalibration must be within 20 mg/dL of the Reference Glucose Value for CGM values less than 100 mg/dL, or within ± 20% of the Reference Glucose Value for CGM values greater than or equal to 100 mg/dL. If a CGM is felt to be inaccurate – cannot be calibrated to meet the aforementioned CGM Validation Criteria – it may be replaced according to the CGM Replacement Criteria.
2. The Dexcom G6 CGM's are greater than 20% different than their averaged value. If the averaged glucose value of the two Dexcom G6 CGM's is greater than 20% different than the CGM values, a Reference Glucose Value will be obtained and both CGM's will be re-calibrated against the result of the Reference Glucose Value using the Dexcom G6 receivers. This recalibration must occur within 5 minutes of obtaining the Reference Glucose Value sample. In this scenario, the FUSION system will automatically alert the clinical study staff of the need to recalibrate both Dexcom G6 CGM's. If the Dexcom G6 Receivers are recalibrated, the matching mobile phone's Dexcom Follow Apps must also be recalibrated at the same time. If a Dexcom G6 CGM is recalibrated, the CGM value one hour after recalibration must be within 20 mg/dL of the Reference Glucose Value for CGM values less than 100 mg/dL, or within ± 20% of the Reference Glucose Value for CGM values greater than or equal to 100 mg/dL.

Prior to starting the closed loop glucose control session, a Reference Glucose Value will be obtained immediately after the time when the CGM sensors begin to return glucose readings. Reference Glucose Values will be subsequently checked every 30 minutes until the CGM sensor values meet the following CGM Validation Criteria:

1. CGM's must be within 20 mg/dL of the Reference Glucose Value for CGM values less than 100 mg/dL, or within ± 20% of the Reference Glucose Value for CGM values greater than or equal to 100 mg/dL.

Closed-loop therapy will begin after two consecutive averages of CGM values meet the above CGM Validation Criteria. The above CGM Validation Criteria will be used throughout the entirety of visit 3.

Blood for independent glucose analysis will be drawn from the retrograde venous line in the warmed hand. The drawn blood will be immediately analyzed for glucose using the Nova StatStrip Hospital Glucose Meter System. These blood glucose values will be known as the Reference Glucose Values. If the arterialized venous line stops working, it may be replaced. If an arterialized venous line is no longer available, fingerstick capillary blood may be used for Reference Glucose Values. Fingerstick capillary blood will be analyzed using the Nova StatStrip Hospital Glucose Meter System.

All Reference Glucose Values will be manually recorded on the studies case report form, however, they will not be used by the FUSION system for purposes of glucose control (except to calibrate the Dexcom G6 CGM's, as necessary).

All subjects will be allowed to drink water throughout the course of the study. No glucose containing drinks will be allowed during the closed loop portion of the study, unless the subjects glucose level (CGM or Reference Glucose Value) is < 70 mg/dL, or the subject is experiencing symptoms of neuroglycopenia. Subjects will remain confined to either the bed or a bedside chair throughout the course of the study. Subjects will use a bedside commode for bathroom breaks in order to prevent any interruption to their closed loop glucose control session.

The following supplies will be needed to complete the study: **1)** four 4-way stopcocks, **2)** two IV tubing (non-microbore) of 6-12 foot length for purpose of attaching the glucose controllers syringe pumps to the subject, **3)** Forty 50 mL BD syringes filled with D10NS (study site research pharmacy to fill these 50 mL syringes using their standard sterile technique), **4)** Six 50 mL BD syringes filled with NovoLog insulin mixed in normal saline to a concentration of 1 unit/mL (study site research pharmacy to fill these 50 mL syringes using their standard sterile technique). The FUSION system (Figure 20) will be supplied by the study sponsor.

8.1.1.5 VISIT 3, TIME 5 TO 29 HOURS (CLOSED LOOP GLUCOSE CONTROL SESSION)

The closed loop glucose control session will not begin until the following criteria has been met:

1. Both Dexcom G6 CGM's are returning glucose values and have been calibrated – if necessary; or replaced – if necessary.

Please refer to the below standard operating procedure (SOP) document for the calibration procedure for the Dexcom G6 CGM's, setting up the FUSION system, and initiating it's software:

FUSION System SOP

To better simulate how the FUSION system will be used in the ICU setting, no run-in period will be performed prior to the subject consuming the first meal. During the 24-hour closed loop glucose control study (time 5 to 29 hours), blood glucose control will be performed autonomously by Ideal Medical Technologies FUSION glucose control system. For safety reasons, the subjects will have a Reference Glucose Value independently measured every 10-60 minutes on the Nova StatStrip Hospital Glucose Meter System. These independent Reference Glucose Values will not be used by the FUSION system for glucose control. After 2-3 hours of confirmed CGM accuracy (e.g., from 0900 to 1200), the closed loop glucose control session will begin. The first meal consumed during the closed loop glucose control session will be lunch.

Lunch will consist of 60 grams of carbohydrate (45-60% of total meal Kcal's) and be consumed beginning at ~1200 hours (the beginning of the closed loop glucose control session). Dinner will consist of 75 grams of carbohydrates (45-60% of total meal Kcal's) and be consumed beginning at 1800 hours (6 hours after beginning of closed loop glucose control session). Breakfast will consist of 50 grams of carbohydrate (45-60% of total meal Kcal's) and be consumed beginning at 0800 hours on day 2 of the closed loop session began (20 hours after the beginning of the closed loop glucose control session).

Subjects will be allowed to have snacks between the hours of 2100 on day 1 and 0600 hours on day 2 of their CRC study, or at any time for CGM or Reference Glucose Values less than 70 mg/dL or for symptoms of neuroglycopenia. Subjects will preselect their breakfast, lunch, and dinner meal choices from the CRC menu prior to the study. These meals will be unannounced to the FUSION system. Once the closed loop glucose control period has ended after 24 hours of glucose control, the control software will be stopped, and the subject will be disconnected from all intravenous infusions.

If the subjects are removed from the study due to the occurrence of a severe hypoglycemic event (< 54 mg/dL), the subjects will have their glucose values measured with a Reference Glucose Analyzer (e.g., Nova StatStrip Hospital Glucose Meter System) every 10 minutes, until their Reference Glucose Values are greater than 70 mg/dL. They will then have additional Reference Glucose Values drawn every 30 minutes, until they have consistent Reference Glucose Values in the range of 80-250 mg/dL for a period of at least two hours. See *Recovery Period* (Pages 107-108) for details with regards to subcutaneous insulin doses to be received prior to discharge from the Clinical Research Center.

The insulin and dextrose 50 mL medication syringes may not be used for more than 24 hours. Although the study should be terminated after a period of 24 hours (e.g., may not go longer than 24 hours), if for any reason the study period is longer than 24 hours (e.g., on orders from the principal investigator), the insulin and dextrose medication syringes must be exchanged for new medication syringes. To be clear, the insulin and dextrose medication syringes may not be used for a period of time exceeding 24 hours.

8.1.1.6 VISIT 3, TIME 29 TO 32 HOURS (OBSERVATION AFTER CLOSED LOOP GLUCOSE CONTROL SESSION)

At the end of the subjects 24 hour closed loop glucose control session, they will be fed lunch consisting of 60 grams of carbohydrate (45-60% of total meal Kcal's). The subjects will resume control of their blood glucose per the protocol instructions (see IMT2022-1-P2) once the closed loop glucose control period has ended. After finishing their lunch, the subjects will continue to have Reference Glucose Values measured every 30 minutes using the Nova StatStrip Hospital Glucose Meter System. When the subjects Reference Glucose Value is in the range of 80-250 mg/dL for a period of at least two hours after the end of their closed loop glucose control session and their most recent glucose rate of change is less than ± 2 mg/dL/min, their intravenous catheters will be removed, and they will be discharged from the CRC. If their blood Reference Glucose Value is less than 80 mg/dL, they will be given additional snacks until their Reference Glucose Value is greater than 80 mg/dL. If the subjects require additional snacks, they will continue to have Reference Glucose Values measured every 30 minutes using the Nova StatStrip Hospital Glucose Meter System until their Reference Glucose Value has been stable in the range of 80-250 mg/dL on four consecutive values and their most recent glucose rate of change is less than ± 2 mg/dL/min, after which time their intravenous catheters will be removed, and they will be discharged from the CRC unit. If their Reference Glucose Value is greater than 250 mg/dl the study's principal investigators (Dr. Pasquel or Dr. Davis) will order a dose of short acting insulin, which will be administered by the clinical study nurse, and their Reference Glucose Value will be monitored every 30 minutes until it is less than 250 mg/dL and their most recent glucose rate of change is less than ± 2 mg/dL/min, at which time they may be discharged from the CRC unit.

8.1.1.7 OTHER

Refer to Protocol 1 (IMT2022-1-P1) for other materials needed to complete the study.
Refer to Protocol 2 (IMT2022-1-P2) for meal challenge in diabetic subjects.

8.1.2 DOSING AND ADMINISTRATION

The dosing of intravenous insulin and intravenous dextrose will be determined by the glucose values measured by the Dexcom G6 continuous glucose monitors, the difference between this measurement and the desired glucose range of 100-140 mg/dL, the glucose rate of change, the current weight based doses of intravenous insulin and/or dextrose that are under the control of the FUSION system, and the rules of Ideal Medical Technologies FUSION glucose control system.

8.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

8.2.1 ACQUISITION AND ACCOUNTABILITY

Ideal Medical Technologies FUSION closed loop glucose control system that is to be utilized in this study will be hand delivered by a representative of Ideal Medical Technologies to the Emory University Clinical Research Center at least two weeks prior to the initiation of the study. This will allow for adequate in-servicing of the principal investigator and all pertinent study personnel as to the use of the complete closed loop glucose control system. The study site will store this system in a secure location so that only study personnel who will be participating in the study will have access to it. After the study has either been completed or cancelled, all equipment supplied to the study site by Ideal Medical Technologies will be immediately returned to Ideal Medical Technologies (at Ideal Medical Technologies expense).

8.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Medical Device Labeling

The medical device under study in this Early Feasibility Study protocol will be labeled as follows:

"Ideal Medical Technologies

18 North Kensington Rd

Asheville, NC 28804

1-828-337-9960

leondej@idealmedtech.com

Storage & Operating temperature of 41-95 F

CAUTION Investigational device. Limited by Federal (or United States) law to investigational use"

8.2.3 PRODUCT STORAGE AND STABILITY

Store and operate all components of medical device under study at room temperatures in range of 41-95 degrees Fahrenheit.

8.2.4 PREPARATION

Not applicable.

8.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

8.4 STUDY INTERVENTION COMPLIANCE

Adherence to the study protocol will be determined through monitoring by Ideal Medical Technologies personnel. In addition, any deviations from the study protocol will be documented on the CRF. Ideal Medical Technologies will review the CRF forms after each study session to ensure adherence to the studies inclusion criteria, exclusion criteria, and for the presence of a signed informed consent document. Please refer to the following document for the studies monitoring plan:

001_IMT_CRC_T1DM_T2DM_Clinical Monitoring Plan

8.5 CONCOMITANT THERAPY

Not applicable.

8.5.1 RESCUE MEDICINE

The study site will supply rescue medication that will be obtained locally. The following rescue medications may be used:

1. 15 mL of 50% Dextrose for intravenous delivery (IV push), every 10 minutes as needed.
2. Glucagon (1 mg/mL) for Intramuscular or intravenous delivery. May give repeat dose 15 minutes after first dose.

The 50% dextrose and Glucagon rescue medications will be used to treat the following conditions:

1) Severe hypoglycemia, which is defined as a Reference Glucose Value less than 54 mg/dL.
2) Moderate hypoglycemia (Reference Glucose Value in the range of 54-69 mg/d) that is accompanied by any of the following neurological signs of hypoglycemia: Anxiety, irritability, sweating, hunger, shakiness, fatigue, pale skin, lethargy, seizures.
3) Neuroglycopenia, which is defined as hypoglycemia of sufficient duration and degree to interfere with normal brain metabolism and function. Neuroglycopenia may occur at Reference Glucose Values greater than or equal to 70 mg/dL. If the subject has signs of hypoglycemia such as anxiety, irritability, sweating, hunger, shakiness, fatigue, pale skin, lethargy, or seizures, they will be treated with 15 mL of 50% Dextrose."

These medications will be hand pushed into the subject's intravenous line by the study nurse or given by intramuscular injection in the case of Glucagon. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded on the case report forms.

In addition to the above rescue medications, in cases of severe hypoglycemia, moderate hypoglycemia with hypoglycemia symptoms, or neuroglycopenia, the subjects will also be offered snacks and glucose containing juices to treat their hypoglycemia and related symptoms.

9 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

9.1 DISCONTINUATION OF STUDY INTERVENTION ON INDIVIDUAL SUBJECT

In the context of this study, termination is defined as the act of bringing either the study on one subject, or the entire study to a permanent end.

On each subject the study will be immediately terminated for any of the following reasons:

A. Termination Criteria for individual subjects:
The study will be terminated on individual subjects if any of the following criteria are met:

1. Subject or their legal authorized representative requests withdrawal from the study for any reason.
2. The clinical study nurses are unable to insert two working Dexcom G6 CGM's prior to beginning the closed loop glucose control session.
3. Subject has a Reference Glucose Value less than 54 mg/dL.
4. Subject has signs of prolonged severe hyperglycemia, as defined by Reference Glucose Value > 240 mg/dL for more than 2 hours.
5. Subject has signs of DKA, as defined by a Reference Glucose Value > 240 mg/dL and blood ketones > 1 mmol/L.
6. CGM or Reference Glucose Value remains > 300 mg/dL for more than 1 hour.
7. FUSION system has only one Dexcom G6 CGM available for use for more than 4 hours.
8. FUSION system has no Dexcom G6 CGM's available for use for more than 20 minutes.
9. There are no Reference Glucose Values for a period of time greater than 60 minutes.
10. The FUSION system experiences any unanticipated adverse device effect (UADE).
11. The subject has had more than 2% of their estimated total blood volume drawn during visit 3.
12. The FUSION system delivers more than 2000 mL (insulin and dextrose infusions) during the 24-hour closed loop glucose control session.

9.2 DISCONTINUATION OF ENTIRE STUDY

A. Termination Criteria for the entire study:
The entire study will be terminated if any of the following criteria are met:

1. Two subjects experience an episode of severe hypoglycemia (Reference Glucose Value < 54 mg/dL) during the time period the FUSION system is in use.
2. Two subjects experience an episode of severe hyperglycemia, as defined by a Reference Glucose Value > 240 mg/dL for more than 2 hours.
3. One subject experiences an episode of DKA after starting the closed loop glucose control session.
4. One subject experiences an episode of HHS after starting the closed loop glucose control session.
5. The FUSION system delivers more than 2000 mL (insulin and dextrose infusions) during the 24-hour closed loop glucose control session in two subjects.
6. The FUSION system experiences any unanticipated adverse device effect (UADE).
7. The study's principal investigator determines that the safety of the studies subjects is being compromised through use of the FUSION system.

If subjects are removed from the study due to hypoglycemia or the development of diabetic ketoacidosis, they will have ongoing monitoring and care in the CRC as noted in Recovery Period (pages 107-108). If a subject signs an informed consent but does not receive closed loop glucose control, they may be replaced. If a subject begins the closed loop glucose control portion of the study, they may not be replaced.

If the study has been terminated on only one subject for a reason other than an unanticipated adverse device effect, the study may continue. If the entire study has been terminated, it may not be resumed until the study's sponsor has submitted study results to the FDA, the study sponsor has presented plans to mitigate the risks that led to the study's termination, and the FDA has approved resumption of the study.

9.3 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

The reason for subject withdrawal or involuntary removal from the study will be recorded on the CRF. If subjects withdraw themselves from the study after starting the closed loop glucose control session, they will be discharged from the CRC after meeting all of the discharge criteria noted in Recovery_Period on page 106. If a subject signs an informed consent but does not receive closed-loop glucose control, they may be replaced. If a subject begins the closed loop glucose control portion of the study, they may not be replaced.

As the study is limited to 32 hours of glucose control/monitoring, no long term follow up will done for the subjects who either complete the study, or for those who are withdrawn for any reason, except as required to record and monitor any adverse events or unanticipated problems.

9.4 LOST TO FOLLOW-UP

Not applicable.

10 STUDY ASSESSMENTS AND PROCEDURES

10.1 EFFICACY ASSESSMENTS

The following procedures/evaluations will be performed on the subjects:

1. Review of medical history and inclusion/exclusion criteria to determine eligibility for the study. This may be performed by any qualified study personnel.
2. Obtain informed consent. This may be performed by any qualified study personnel.
3. Draw blood for creatinine, alanine aminotransferase, hemoglobin, HbA1c, and C-peptide. These labs will be analyzed in the hospital's central laboratory. For women of childbearing age of 18-55 years inclusive, obtain a urine pregnancy test. Blood draw will be performed by any qualified personnel. If these results have already been obtained as part of the subject's routine laboratory studies, the already obtained results may be used to assess the subject for inclusion/exclusion criteria.
4. For subjects who have signed an informed consent and whose lab results do not exclude them from the study, an appointment for visit 3 will be set. This appointment must occur within 2 weeks of the date the informed consent was signed.
5. During visit 3, the subject will undergo closed loop control of their blood glucose level from time 5 to 29 hours utilizing Ideal Medical Technologies FUSION closed loop glucose control system. Refer to the SOP for set up, initiation and use of this system. To initialize the glucose control software the study RN will enter the patient's weight (Kg), study identification number, and initial Reference Glucose Value. The glucose control range of 100-140 mg/dL will be automatically defaulted to by the glucose control software. On initiation of the closed loop glucose control session the study RN will obtain a blood sample for glucose analysis from the arterialized retrograde intravenous line every 30 minutes. This blood sample will be immediately analyzed for a Reference Glucose Value on the Nova StatStrip Hospital Glucose Meter System. Results from this test will be entered into the appropriate case report form as soon as it becomes available. The frequency of checking Reference Glucose Values is outlined in the study protocol on pages 102-103. The study RN will be responsible for making sure the insulin and dextrose syringes in the syringe pumps being used for glucose control remain at least 20% full (at least 10 mL volume remaining in 50 mL BD syringe) throughout the course of the closed loop glucose control study.
6. A total of approximately 60 blood draws for glucose analysis will be obtained during the study. The blood volume removed with each blood draw will be 0.5 mL, for a total blood loss of no more than 40 mL's. This is in addition to the 10 mL removed previously for lab analysis to verify eligibility for the study. The total volume of blood removed from the subject for purposes of completing this study should be less than 80 mL's over a period of 2 weeks.
7. At the conclusion of the study the two Dexcom G6 CGM's and the two intravenous lines will be removed from the subject by the study clinical nurse. The subjects will be discharged from the CRC when they have met the discharge criteria noted in the study protocol (IMT2022-1-P2).

The subjects who have participated in the study will be given the following information after conclusion of the study:

1. Their average glucose value over the period of closed loop glucose control.
2. Their CV value over the period of closed loop glucose control.
3. Their percent time in range < 70 mg/dL over the period of closed loop glucose control.
4. Their percent time in range 70-180 mg/dL over the period of closed loop glucose control.
5. Their percent time in range > 180 mg/dL over the period of closed loop glucose control.

10.2 SAFETY AND OTHER ASSESSMENTS

10.2.1 SAFETY

The exclusion criteria which are used to screen for potential subjects eliminates those with hepatic failure, signs of significant hepatic disease as defined by an alanine aminotransferase greater than three times the upper limit of normal, any signs of renal failure, subjects with any history of congestive heart failure, subjects with a history of ischemic heart disease/cerebrovascular accident/seizures and eliminates all females who are pregnant. The purpose of these exclusion criteria is to avoid first in human trials on subjects with severe organ compromise, and exposure of a fetus to an untested medical device.

Independently monitoring Reference Glucose Values every 10-60 minutes will ensure subject safety should they experience hypoglycemia that the closed loop glucose control system is either unaware of or is unable to effectively treat. This monitoring will allow for early intervention in case the subjects experience severe hypoglycemia (Reference Glucose Value < 54 mg/dL) or moderate hypoglycemia (Reference Glucose Value 54-69 mg/dL) with clinical signs of hypoglycemia.

10.2.2 PHYSICAL EXAM/LABS

The visit 1 physical exam will be limited to recording the subject's weight. No vital signs will be recorded. During the closed loop glucose control portion of the study the subject's vital signs will be monitored with a frequency of at least every 1 hour.

No EKG's will be needed for purposes of completing this study. No radiologic studies will be needed for purposes of completing this study.

The screening labs which are part of the exclusion criteria will be performed in the central laboratory. The blood for these labs will be stored as per institution specific guidelines as the study itself does not require that the blood used for these studies be stored for any length of time. The overall blood volume needed for purposes of completing the study is estimated to be approximately 50 mL but may be as much as 80 mL.

10.2.3 SPECIAL ASSAYS

The Reference Glucose Values to be done at the bedside will be performed on a Nova StatStrip Hospital Glucose Meter System. The study personnel will require specialized training on use of the Nova StatStrip Hospital Glucose Meter System, if they have not previously been trained on its use.

10.2.4 USE OF EXISTING MEDICAL RECORD DATA

For purposes of performing the screening criteria the existing medical records available at the time of the subject's routine visit to the adult endocrinology clinic will be used whenever possible. In addition to medical history and physical exam information, this may also include use of necessary lab work to include creatinine, alanine aminotransferase, hemoglobin, HbA1c, C-peptide, and urine pregnancy test.

10.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

10.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

10.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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, 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 or be life-threatening may be considered serious when, based upon appropriate medical judgment, they may jeopardize the

participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.3.3 CLASSIFICATION OF AN ADVERSE EVENT

10.3.3.1 SEVERITY OF EVENT

For adverse events (Aes) not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- **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". For purposes of this study, the following will be considered severe adverse events:

1. Death
2. A life threatening experience
3. Persistent or significant disability/incapacity
4. Seizure secondary to hypoglycemia
5. Myocardial infarction that is temporally related to a hypoglycemic (< 70 mg/dL) event
6. Cardiac dysrhythmia that that is temporally related to a hypoglycemic (< 70 mg/dL) event
7. Reference Glucose Value < 54 mg/dL
8. Diabetic Ketoacidosis: meeting all criteria: symptoms such as polyuria, polydipsia, nausea, or vomiting, serum ketones > 1.5 mmol/L, either arterial blood pH < 7.30 or venous pH < 7.24, or serum bicarbonate < 15. DKA is suspected as either the primary or a contributing cause for these findings.
9. Considered severe for any other reason.

Study site personnel must alert Ideal Medical Technologies Inc. or its designee of any severe adverse event (SAE) within 48 hours of investigator awareness of the event via an agreed upon method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. See attachment IMT2022-1-A1 for serious adverse event form.

10.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (Aes) must have 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 of a medical device, the medical device under study 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.

10.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

10.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or severe adverse event (SAE) may come to the attention of study personnel during study visits or upon review by a study monitor.

All Aes including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to medical device under study (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.

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. However, if the study participant's condition deteriorates 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.

The Principal Investigator or his designee will record all reportable events with start dates occurring any time after informed consent is obtained until 1 (for non-serious Aes) or 3 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Unsolicited adverse events are not applicable to this study.

10.3.5 ADVERSE EVENT REPORTING

Adverse events will be reported by the Principal Investigator to the Institutional Review Board and study sponsor if in the opinion of the Principal Investigator the adverse event was caused by or related to use of the medical device under study.

10.3.6 SERIOUS ADVERSE EVENT REPORTING

If during the course of this study a serious adverse event occurs, the Principal Investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) 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 Food and Drug Administration (FDA), the IRB and the Principal Investigator 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.

10.3.7 REPORTING EVENTS TO PARTICIPANTS

Adverse Events and Serious Adverse Events will be reported to the participants of this study if in the opinion of the Principal Investigator they are related to the medical device under study.

10.3.8 EVENTS OF SPECIAL INTEREST

Any medical device malfunction that either impedes or prevents the carrying out of this study will be reported to the sponsor, IRB, and regulatory agencies.

10.3.9 REPORTING OF PREGNANCY

If during the course of this study, a subject has signed an informed consent and is found to be pregnant prior to the treatment phase of the study, this subject will be informed of the positive pregnancy test and the fact that this excluded them from the treatment phase of the study.

10.4 UNANTICIPATED PROBLEMS

10.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems will be considered those that involve risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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, a device, 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.

10.4.2 UNANTICIPATED PROBLEM REPORTING

The Principal Investigator will report unanticipated problems (Ups) to the sponsor and the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

This report shall be submitted as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. A sponsor who conducts an evaluation of an unanticipated adverse device effect shall report the results of such evaluation to the FDA, the reviewing IRB, and to the Principal Investigator 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.

10.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

11 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will not be developed for this study, thus formal null and alternative hypothesis will not be stated.

11.1 STATISTICAL MEASUREMENTS

Primary Safety and Efficacy Endpoints:

1. Safety

The safety of the FUSION system will be determined by its ability to avoid hypoglycemia in adult type 1 and type 2 diabetic patients consuming three meals over a period of 24 hours. Safety will be measured by calculating the percent of all glucose values that are within the hypoglycemic range of less than 70 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

2. Efficacy

The efficacy of the FUSION system will be determined by its ability to maintain glucose in the normal range in adult type 1 and type 2 diabetic patients consuming three meals over a period of 24 hours. Efficacy will be measured by calculating the percent of all glucose values that are within the normal glucose range of 70-180 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

Secondary Efficacy Endpoints:

The secondary objectives of the study are to assess the controller's ability to minimize glucose curve measurements associated with increased ICU morbidity/mortality rates, and to maximize those measurements associated with decreased ICU morbidity/mortality rates.

1. Measure the percent of glucose values that are within the severe hypoglycemic range of 0- <54 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

2. Measure the percent of glucose values that are within the moderate hypoglycemic range of 54-69 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

3. Measure the number of hypoglycemic (< 70 mg/dL) events.

Statistics – No statistical comparison will be made for this measurement.

4. Measure the percent of all glucose values that are within the desired glucose control range of 100-140 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

5. Measure the percent of glucose values that are within the range of 70-140 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

6. Measure the percent of glucose values that are within the hyperglycemic range of > 140 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

7. Measure the percent of glucose values that are within the range of 70-180 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

8. Measure the percent of glucose values that are within the hyperglycemic range of > 180 mg/dL.

Statistics – No statistical comparison will be made for this measurement.

9. Measure the mean glucose value in mg/dL.

Statistics – No statistical comparison will be made for this measurement.

10. Measure of dispersion – coefficient of variation.

Statistics – No statistical comparison will be made for this measurement.

11. The study data will be used to determine the percentage of paired glucose values (continuous glucose monitors and the average of the two continuous glucose monitors versus the Nova StatStrip Hospital Glucose Meter System Reference glucose) in each zone using a Clarke error grid analysis.[1] No statistical comparison will be made for this measurement.

The glucose data for the above statistical analysis will be the glucose data used by the FUSION system for purposes of glucose control, unless otherwise specified.

11.2 SAMPLE SIZE DETERMINATION

As this is a first in human study of a medical device a statistically determined sample size was not used. Rather, the subject number of eight was chosen as it is consistent with the FDA's recommended number of 6-10 subjects for a first in human study of a medical device.

The anticipated dropout rate after subjects have begun closed loop glucose control is less than 10%, which should not significantly affect the study results. No interim analysis is planned. Given the small sample size no subgroup analysis is planned.

11.3 POPULATIONS FOR ANALYSES

Not applicable. All subjects who begin closed loop glucose control will be used for analysis.

11.4 STATISTICAL ANALYSES

11.4.1 GENERAL APPROACH

The data will be presented as median and interquartile range (25-75), except for the Clarke error grid analysis which will be presented as percent of values in zones A, B, C, D and E.

11.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

1. To determine percent time in range < 70 mg/dL for each subject, the calculation is as follows:

(# of glucose values in range < 70 mg/dL**/**total number of all glucose values) * 100

This result will be presented as median and interquartile range (25-75).

2. To determine percent time in range 70-180 mg/dL for each subject, the calculation is as follows:

(# of glucose values in range 70-180 mg/dL**/**total number of all glucose values) * 100

This result will be presented as median and interquartile range (25-75).

11.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For the secondary endpoints that measure percent time in range, the values will be calculated as noted above in 9.4.2. These results will be presented as median and interquartile range (25-75).

The number of hypoglycemic events less than 70 mg/dL will be presented as median and interquartile range (25-75).

The mean glucose level will be presented as mean ± SD.

The coefficient of variation will be presented as median and interquartile range (25-75).

The Clarke error grid analysis will be presented as a graph of the Clarke error grid. The Reference Glucose Value (Nova StatStrip Hospital Glucose Meter System) and Dexcom G6 data will be analyzed to determine the percent of all values that are in zones A, B, C, D and E.

11.4.4 SAFETY ANALYSES

For the safety primary endpoint of percent time in range < 70 mg/dL, the calculation is as follows:

(# of glucose values in range < 70 mg/dL/total number of all glucose values) * 100

This result will be presented as median and interquartile range (25-75).

Each AE or SAE will be independently reported as percent of patients experiencing the event. SAE's that require stopping the study prematurely will be separately reported in a table. If the principal investigator feels the AE or SAE's are secondary to the intervention this will be reported in the final study summary. Any rescue medicine that is used per 8.5.1 will be separately reported as percent of subjects requiring rescue medicine.

11.4.5 BASELINE DESCRIPTIVE STATISTICS

The following baseline characteristics will be recorded at the start of the study, **1)** age, **2)** sex, **3)** duration of diabetes (years), **4)** diabetes therapy at time of CRC study [e.g., insulin, oral anti-hyperglycemic + insulin], **5)** HbA1c level, **6)** C-Peptide level, **7)** Height (cm), **8)** Body weight (Kg), **9)** body mass index [BMI], **10)** starting blood glucose (mg/dL), **11)** Estimated Total Blood Volume.

11.4.6 PLANNED INTERIM ANALYSES

Planned interim analysis- None.

11.4.7 SUB-GROUP ANALYSES

Not applicable.

11.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

11.4.9 EXPLORATORY ANALYSES

None planned.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1.1 INFORMED CONSENT PROCESS

12.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

IMT2022_1_Informed Consent Form_CRC_8 Subjects

12.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be

informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

For subjects who are not native English speakers, a study site provided medical translator will be made available for purposes of reviewing the informed consent document and answering any questions the subject has with regards to the study or the informed consent document. Family members will not be allowed to serve as translators.

12.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the Institutional Review Board, the Investigational Device Exemption (IDE)/study sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA.

12.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of

biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or medical device company supplying the medical device may inspect all documents and records required to be maintained by the Principal Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records that are pertinent to the study, for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Emory University Healthcare. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by Emory University Healthcare research staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived at Emory University Healthcare.

12.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

12.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Francisco J Pasquel, MD, MPH Associate Professor of Medicine	Dr. Leon DeJournett Chief Medical Officer

Division of Endocrinology, Metabolism, and Lipids	
Emory University School of Medicine	Ideal Medical Technologies
Emory University School of Medicine Division of Endocrinology, Metabolism, and Lipids 69 Jesse Hill Jr Drive SE Atlanta, GA 30303	Ideal Medical Technologies 18 N Kensington Rd Asheville, NC 28804
404-778-1695	828-337-9960
fpasque@emory.edu	leondej@idealmedtech.com

12.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an Independent Safety Monitor (ISM) who will be a nurse with relevant expertise, whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study. The ISM will provide input to both the Principal Investigator and the IRB. The ISM will be an employee of Emory University.

12.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

- Ideal Medical Technologies will provide an in-service to study personnel in order to ensure safe use of its FUSION closed loop glucose control system. IMT personnel will be immediately

available to answer any questions pertaining to the study protocol or the FUSION system. If IMT personnel are present on site during the 24 hour closed loop glucose control session, they will not interact with participants or their identifiable data. All study records will undergo a comprehensive review (100% data verification) by an Ideal Medical Technologies representative after completion of each study session to verify ongoing adherence to the study protocol. This review may occur remotely and must be completed prior to continuing with the subsequent study sessions. This review will include a monitoring report that will be sent to the PI via email prior to continuing with the study. Any issues raised during this review process must be addressed by the PI prior to continuing with the study.

- Independent audits will not be conducted.

The formal monitoring plan can be seen in the following document:

IMT2022_1_CRC_T1DM_T2DM_Clinical Monitoring Plan

12.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., GLP, Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.1.9 DATA HANDLING AND RECORD KEEPING

12.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (Aes), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a FDA compliant data capture system provided by Emory University Healthcare. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the IDE/study sponsor. It is the responsibility of the IDE/study sponsor to inform the investigator when these documents no longer need to be retained.

12.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents and reported to the study sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements. The protocol deviations will also be reported to the FDA as required.

12.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. This study will be registered with ClinicalTrials.gov.

For any peer reviewed articles submitted for publication that arise out of the results of this study, the Principal Investigator or the Principal Investigators designated co-investigator will serve as lead author. In addition, the following two Ideal Medical Technologies (sponsor) employees will also be named authors of any and all publications that arise out of the results of this study:

1. Jeremy DeJournett
2. Leon DeJournett

12.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Conflicts of interest:

Leon DeJournett – Owns stock in Ideal Medical Technologies.

Jeremy DeJournett – Owns stock in Ideal Medical Technologies.

12.2 ADDITIONAL CONSIDERATIONS

This section should include a description of any additional considerations not currently covered in this protocol template, such as particular institutional or IRB-related requirements.

12.2.1 DATA IDENTIFICATION

Subjects who have signed an informed consent will be assigned a unique identification number that will remain the same throughout the study. This identification number will be used to identify the subject, for purposes of initiating the FUSION system at the start of the study. This number will be visible on the FUSION systems graphical user interface throughout the 24 hour closed loop glucose control session and will be the only subject identifier displayed on the FUSION systems graphical user interface. The FUSION systems graphical user interface will not display any information that could be used to directly identify the subject (e.g., name, date of birth, social security number). This study will use only de-identified data.

12.2.2 ROLE OF IDEAL MEDICAL TECHNOLOGIES PERSONNEL IN STUDY

Ideal Medical Technologies personnel will be available throughout the 24 hour closed loop glucose control session to assist the study personnel with use of the FUSION system. This assistance will be limited to the following:

1. Explanation of the components of the FUSION system including the connecting cables and power cords
2. Explanation of the powering up process of the FUSION system
3. Explanation of how to use the two syringe pumps that are part of the FUSION system
4. Explanation of how to load the insulin and dextrose medication syringes into the two syringe pumps
5. Explanation of how to change the medication syringes used in the syringe pumps
6. Explanation of the proper set up of the medication (e.g., insulin and dextrose) and carrier solution (e.g., ½ NS) intravenous lines
7. Explanation of how to enter the data needed to initiate the FUSION system (e.g., unique identification number and weight in kg)
8. Explanation of how to start the closed loop glucose control session
9. Explanation of how to pause the closed loop glucose control session
10. Explanation of how to end the closed loop glucose control session
11. Explanation of how to extract study data from the FUSION system at the end of the closed loop glucose control session
12. Explanation of how to power down the FUSION system
13. Explanation of how to properly store the FUSION system

Ideal Medical Technologies personnel will not attempt to interact with the study subjects in any way. Ideal Medical Technologies personnel will provide no medical care for the study subjects. Ideal Medical Technologies personnel will not personally extract the study data from the FUSION system. Ideal Medical Technologies personnel will not analyze the study data (this analysis will be performed by Emory University study personnel).

12.3 ABBREVIATIONS

AE	Adverse Event
AI	Artificial Intelligence
ALT	Alanine Aminotransferase
AP	Artificial Pancreas
BD	Becton Dickinson
BMI	Body Mass Index
CGM	Continuous Glucose Monitor
CM	Centimeter
CRC	Clinical Research Center
CRF	Case Report Form
CT	Computerized Tomography

CV	Coefficient of Variation
dL	Deciliter
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EFS	Early Feasibility Study
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HbA1c	Hemoglobin A1c (glycosylated hemoglobin)
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
iCGM	Integrated continuous glucose monitor
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IMT	Ideal Medical Technologies
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
IV	Intravenous
KBS	Knowledge Based System
KDS	KD Scientific
Kg	Kilogram
L	Liter
LOS	Length of Stay
mg	Milligrams
mg/dL	Milligrams/deciliter
MIMO	Multiple Input Multiple Output
min	Minute
mL	Milliliter
mL/kg/hour	Milliliters/kilogram/hour
mM	Millimole
mmol	Millimole
mmol/L	Millimole/Liter
MOP	Manual of Procedures
MPC	Model Predictive Control
n	Number
NA	Not Applicable
NIH	National Institutes of Health
NYHA	New York Heart Association
P	Probability
PD	Proportional Derivative
PI	Principal Investigator
PID	Proportional Integral Derivative

QA	Quality Assurance
QC	Quality Control
RN	Registered Nurse
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Sensor Error
SOA	Schedule of Activities
SOP	Standard Operating Procedure
STAT	Immediately
TIR hi	Time In Range high
TIR lo	Time In Range low
units/kg/hour	Units/Kilogram/hour
unit/mL	Unit/Milliliter
UP	Unanticipated Problem
USA	United States
YSI	Yellow Springs Instrument
%	Percent

12.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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Protocol 1 – Preparation of Subject for Visit 3

(IMT2022-1-P1)

ii. Study Materials (Visit 3)

The following materials will be available in the subject's CRC room for purposes of performing the closed loop glucose control study.

A) Six 50 mL BD syringes filled with NovoLog insulin mixed in normal saline to a concentration of 1 unit/mL (study site research pharmacy to fill these 50 mL syringes using their standard sterile technique). Must be available by 1200 hours on day of CRC study.

B) Forty 50 mL BD syringes filled with D10 normal saline (study site research pharmacy to fill these 50 mL syringes using their standard sterile technique). Must be available by 1200 hours on day of CRC study.

C) One 500 mL bags of normal saline and one 500 mL bag of one-half normal saline and associated intravenous tubing needed to infuse via an intravenous pump.

D) Two intravenous pumps (these are in addition to the IMT supplied syringe pumps used by the FUSION system).

E) One hundred TB syringes for purposes of withdrawing blood from the arterialized hand vein.

F) Nova StatStrip Hospital Glucose Meter System Glucose Hospital Meter System, including at least 100 glucose test strips.

G) Nova Max Plus ketone meter (Nova Biomedical) and associated ketone test strips.

H) FUSION glucose control system (20) to be provided by the studies sponsor at least 2 weeks prior to the studies onset.

I) Four 6-12 foot lengths of non-microbore intravenous tubing for purposes of infusing solutions (e.g., insulin, D10NS, ½ NS, NS) into the subject.

1.2 Continuous Intravenous Infusion Set Up

A) Run one-half normal saline at 10 mL/hour via the peripheral IV that will be used to infuse the insulin and/or D10NS from the FUSION system. Refer to below diagram (Figure 26) for the setup of the ½NS, insulin, and dextrose lines. The intravenous tubing used for the insulin infusion should be flushed with 50 mL of insulin solution prior to being connected to the peripheral IV.[92] Run normal saline at 10 mL/hour via the retrograde peripheral IV to maintain patency between blood draws.

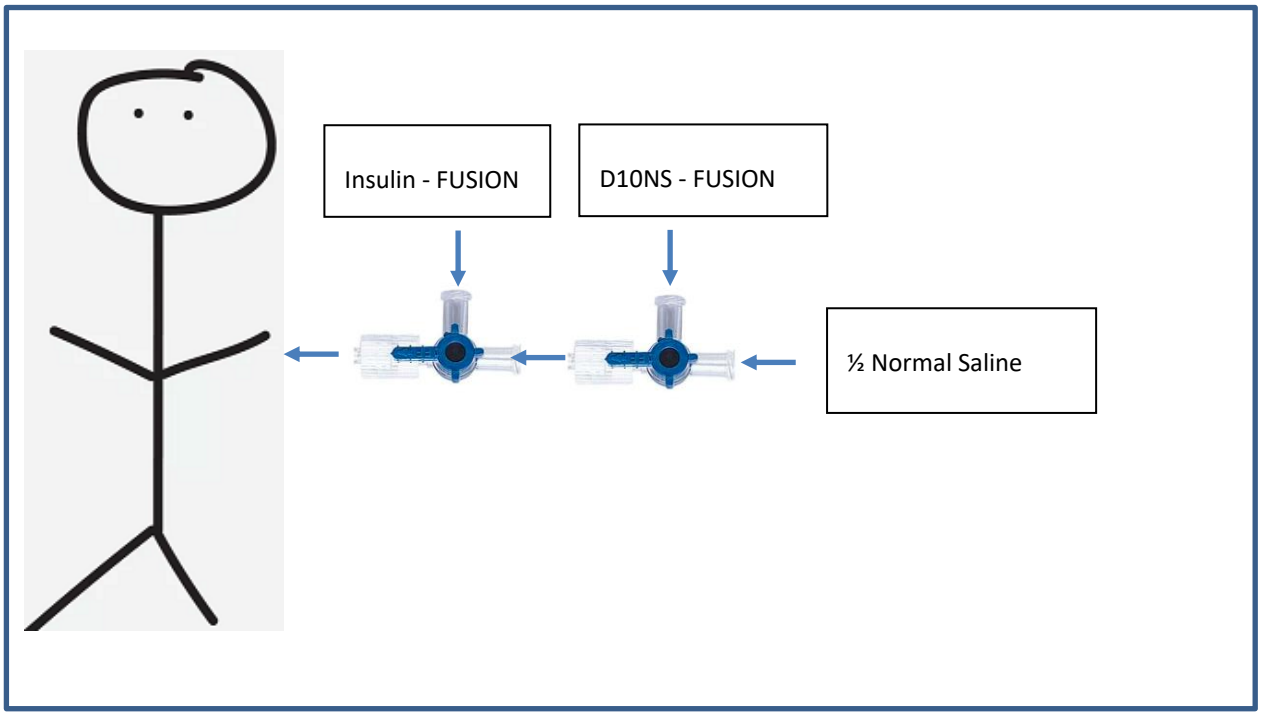


Figure 26 – Illustration of set up of insulin, dextrose, and normal saline infusions for the FUSION closed loop glucose control system.

Protocol 2 – Meal Challenge in Type 1 and Type 2 Diabetic Subjects

(IMT2022-1-P2)

MEAL CHALLENGE PROTOCOL

Type 1 and Type 2 diabetic subjects will be admitted to the CRC between 0600 to 0700 hours after an overnight fast.

Methods Overview:

After admission to the CRC and confirming the subjects are eligible to continue with the closed loop glucose control session on visit 3 (see pages 53-54), catheters will be placed in one antecubital vein for purpose of insulin and or D10NS infusion, and in a contralateral arm vein in a retrograde fashion for purposes of blood draws.

Precaution to Avoid Electrostatic Discharge from Affecting FUSION System

Touching the FUSION system when your body has a build-up of static electricity may cause an electrostatic discharge (e.g., flow of electricity) into the FUSION system. It is unknown if this would adversely affect the performance of the FUSION system. In order to mitigate against the risk of study personnel introducing an electrostatic discharge into the FUSION system, the following precaution must always be taken prior to touching the FUSION system:

1. Touch a metal table that is positioned near the FUSION system but is not in contact with the subject or the FUSION system. This procedure must be performed prior to each interaction (e.g., touching) with the FUSION system.

Meal Challenge Protocol:

The meal challenge protocol is outlined in detail below.

Potential Problems.

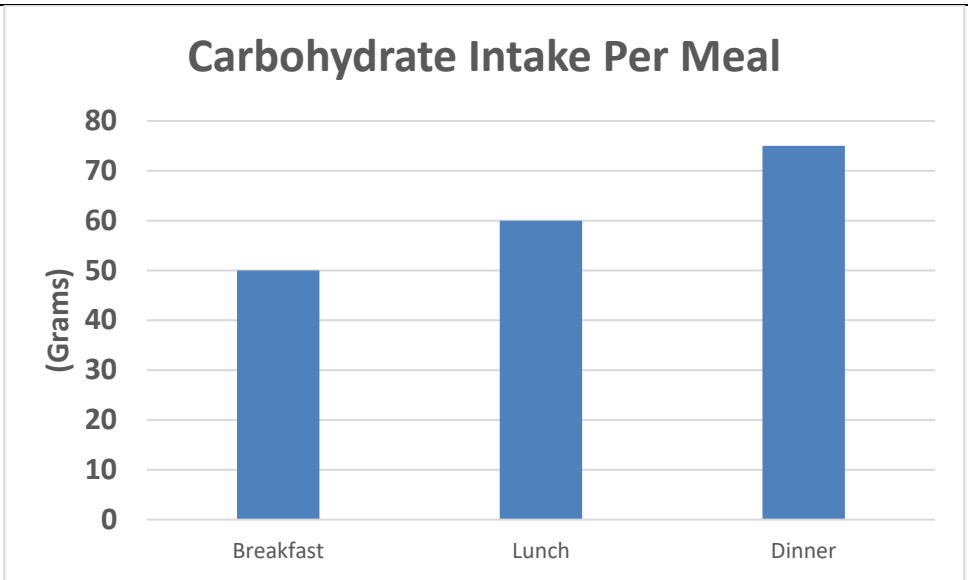
Severe hypoglycemia (< 54 mg/dL) may be associated with adrenergic response symptoms (tachycardia, sweating, palpitations) and neuroglycopenia symptoms (impaired cognition, coma, seizures). Based upon previous studies, patients can sustain hypoglycemia for approximately 30 min to an hour.

To avoid risk to our human subjects, vital signs will be monitored closely. Frequent independent glucose measurements will be performed (every 10-60 minutes) to minimize the risk of severe hypoglycemia (< 54 mg/dL) or moderate hypoglycemia (54-69 mg/dL) with the above noted hypoglycemia symptoms. The protocol calls for rescue doses of 15 mL of 50% dextrose for severe hypoglycemia, moderate hypoglycemia with hypoglycemia symptoms, or neuroglycopenia. In addition, the study on any one subject will be terminated if they experience a severe hypoglycemia event (< 54 mg/dL). The overall study will be terminated if two subjects experience a severe hypoglycemia event (< 54 mg/dL).

Patients with a history of liver failure, renal failure, cerebrovascular accident, seizure disorder, congestive heart failure, and ischemic heart disease will not be recruited for this study.

During the time period when the FUSION system is operational and active, if a participant's CGM or Reference Glucose Value is >240 mg/dL for over 1 hour or ≥ 300 mg/dL at any point after starting the FUSION system, the following steps will be taken: Ketones will be assessed at the discretion of the principal investigator(s) for any concern about possible ketosis or DKA by checking a blood ketone level at the bedside. If the blood ketone level is greater than 1 mmol/L, a venous blood sample from the subject will be sent to the central laboratory of Emory Healthcare for a basic metabolic panel, blood pH, and beta hydroxybutyrate level. If the subject is found to be in DKA, the subject will be stabilized per the usual routine care at Emory Healthcare.

When a hyperglycemia/ketotic event meets the above reporting requirements, an Adverse Event Form will be completed. Events meeting DKA criteria should be considered serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the severe adverse event criteria is met.

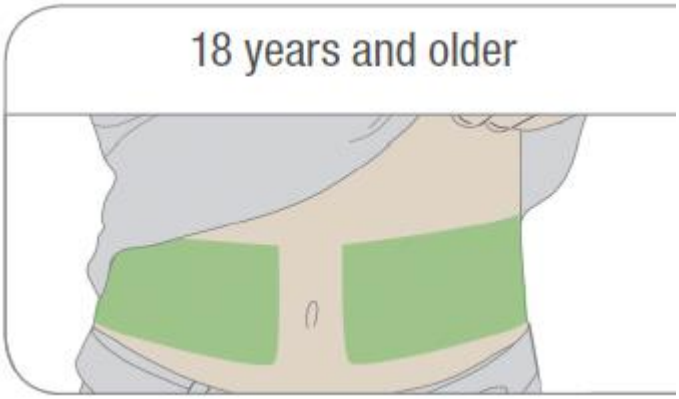
Meal Challenge Protocol Detailed	
	 ***Figure 27 – Carbohydrates should represent 45-60% of total Kcal's for each meal. The total carbohydrates consumed at breakfast, lunch and dinner will be 50, 60 and 75 grams.***
1.	Admit to Study Site on (specify date) _____ between 06:00-07:00AM.
2.	Informed Consent ___ Signed and in the Medical Chart. ___ Must be signed upon Admission prior to any procedure.
3.	**Ad Lib water prior to Closed Loop Glucose Control** Instruct subject to void. Subject may have ad lib water throughout their entire stay in the CRC.
4.	**Voiding during the CRC visit (time 0-32 hours)** The subject may use the bathroom for voiding prior to the onset of the closed loop glucose control session (time 0-5 hours), and after conclusion of the closed loop glucose control session (time 29-32 hours). If subject needs to void during the closed loop glucose control session (time 5-29 hours), a bedpan/urinal must be provided, in order to make sure the subjects blood glucose level remains under the control of the FUSION system.
5.	**Diet before study onset (time -7 to 1 hours):** Fast between 00:00 hours (e.g., midnight) on day of closed loop study and time of breakfast at 0800 hours on day 1.
6.	**Research staff to calibrate and Quality Control the Nova StatStrip Hospital Glucose Meter System**

7.	**Screening prior to initiation of the closed loop glucose control session (time 0-1 hours)** The subjects will be tested for the presence of diabetic ketoacidosis and appropriate Reference Glucose Values prior to proceeding with the closed loop glucose control session. This testing will include: i. Reference Glucose Value at time of admission to the CRC – If the Reference Glucose Value is greater than 300 mg/dL, the subject will be screened for blood ketones using the Nova Max Plus (Nova Biomedical) ketone meter. If the Reference Glucose Value is less than 70 mg/dL or the subjects are experiencing any symptoms of hypoglycemia, regardless of their blood Reference Glucose Value, the subjects will be offered a snack or glucose containing juice. To be clear, the Nova Max Plus ketone meter will be used for any blood ketone analysis performed during the time the subjects are in the CRC. ii. Blood ketones – The study will be cancelled if the blood ketones are > 1 mmol/L. If blood ketones are > 1 mmol/L, a venous blood sample will be sent to the central lab at Emory University for a basic metabolic panel, venous pH and beta-hydroxybutyrate to rule out diabetic ketoacidosis. If diabetic ketoacidosis is confirmed, the participant will be stabilized per the usual routine care at Emory Healthcare. iii. Blood glucose prior to insertion of Dexcom G6 CGM's and intravenous lines – The subjects Reference Glucose Value must be in the range of 70-300 mg/dL prior to insertion of the two Dexcom G6 CGM's and two intravenous lines. In addition, the closed loop glucose control session will not be initiated if the participant has symptoms requiring action (e.g., abdominal pain, vomiting, unable to eat or drink, fever ≥ 101.5), regardless of blood glucose or ketone levels.
8.	**Diet before onset of closed loop glucose control session (time 0-5 hours):** Subject to be offered breakfast with 50 grams of carbohydrate at time 1 hours (~ 0800 hours on day 1), after admission to the CRC unit. After consuming breakfast, the subject is to remain NPO until lunch offered at the time of initiation of the closed loop glucose control session at time 5 hours (~ 1200 on day 1). After admission to the CRC, if the subject has a Reference Glucose Value less than 70 mg/dL or is experiencing signs of neuroglycopenia (hypoglycemia of sufficient duration and degree to interfere with normal brain metabolism and function) at any Reference Glucose Value, they will be offered snacks and/or glucose containing juice.
9.	**Insulin Dosing Prior to Study Onset (time 0-5 hours):** The study's principal investigators (Dr. Pasquel or Dr. Davis) will determine the short acting insulin dose required to cover the breakfast that is consumed at approximately 0800 hours on Day 1, based on the subject's medical history, pre-prandial Reference Glucose Value that is measured by the Nova StatStrip Hospital Glucose Meter System from a fingerstick capillary sample, and carbohydrate load in the meal. All insulin doses given during the CRC stay (visit 3) will be administered by a

	research nurse and will be documented in the subjects Electronic Health Record. The Emory Clinical Research Center will provide all insulin that is administered to the subjects throughout visit 3 (e.g., the subject may not use their own insulin during visit 3).
10.	**Body Measurements:** Weight: _____ kg Height: _____ cm
11.	**Two IV Catheters placements:** - One antecubital intravenous line (for infusion of insulin and dextrose) with an 18-20 gauge catheter with two 3-way gang stopcock (insulin from FUSION system in first stopcock, dextrose from FUSION system in second stopcock). First stopcock closest to subject, second stopcock furthest from subject. - One IV (18-20 gauge catheter) in contralateral hand (from antecubital IV) placed in a retrograde fashion for purposes of blood draws. This hand to be warmed as noted below. - Study nurse to inspect IV sites on an hourly basis, or whenever subject complains of pain at IV site. - **A. Run ½ normal saline at 10 mL/hr using a standard IV pump through the IV line used to infuse insulin and/or dextrose from the FUSION system.** **B. Run normal saline at 10 mL/hr using a standard IV pump through the retrograde hand IV line used for blood draws.**
12.	**Warming of retrograde hand vein to 50-55 °C** Arm with retrograde hand IV that is to be used for blood sampling will be kept warm by use of a heating pad or similar device to increase blood flow in order to achieve "arterialized" samples.[93]
13.	**Monitoring Activities:** **A. Vital signs (Every 4 hours throughout the entire CRC stay)**: Temp _____ RR _____ HR _____ Time of collection: _____:_____ BP _____ / _____ Time of collection: _____:_____ Document the vital signs on the case report form. **B. Assessment of IV sites (Every 1 hour during closed loop glucose control session):** Assess for signs of infiltration as evidenced by local swelling or pain at IV insertion site. Assess for signs of bleeding. Document these assessments on the case report form. **C. Assessment for fluid overload (Every 2 hours during closed loop glucose control session):** Assess for signs of fluid overload that will be manifested as peripheral edema (swelling of hands, feet, legs, or eyelids), shortness of breath, and rales on auscultation of lungs. Document these assessments on the case report form. **D. Assessment of CGM insertion sites (Every 4 hours from time 4 to 32 hours):** Assess for local signs of skin irritation, bleeding, or infection. **E. Assessment for development of DKA, Severe Hyperglycemia, or HHS**

	Assess for the development of DKA, severe hyperglycemia (> 240 mg/dL), or HHS by obtaining Reference Glucose Values at least every 1 hour. The study will have termination criteria (see below) that will terminate the study on the subject if they are showing signs of DKA, severe hyperglycemia, or HHS.
14.	**Termination Criteria** **A. Termination Criteria for individual subjects:** The study will be terminated on individual subjects if any of the following criteria are met: 1. Subject requests withdrawal from the study for any reason. 2. The clinical study nurses are unable to insert two working Dexcom G6 CGM's prior to beginning the closed loop glucose control session. 3. Subject has a Reference Glucose Value less than 54 mg/dL. 4. Subject has signs of prolonged severe hyperglycemia, as defined by Reference Glucose Value > 240 mg/dL for more than 2 hours. 5. Subject has signs of DKA, as defined by a Reference Glucose Value > 240 mg/dL and blood ketones > 1 mmol/L. 6. Subject has signs of HHS, as defined by a Reference Glucose Value > 300 mg/dL for more than 1 hour. 7. FUSION system has only one Dexcom G6 CGM available for use for more than 4 hours. 8. FUSION system has no Dexcom G6 CGM's available for use for more than 20 minutes. 9. There are no Reference Glucose Values for a period of time greater than 60 minutes. 10. The FUSION system suffers any unanticipated adverse device effect (UADE). 11. The subject has had more than 2% of their estimated total blood volume drawn during visit 3. 12. The FUSION system delivers more than 2000 mL (insulin and dextrose infusions) during the 24-hour closed loop glucose control session. **B. Termination Criteria for the entire study:** The entire study will be terminated if the following criteria are met: 1. Two subjects experience Reference Glucose Values < 54 mg/dL during the time period the FUSION system is in use. 2. Two subjects experience an episode of severe hyperglycemia, as defined by a Reference Glucose Value > 240 mg/dL for more than 2 hours. 3. One subject experiences an episode of DKA after starting the closed loop glucose control session. 4. One subject experiences an episode of HHS after starting the closed loop glucose control session. 5. The FUSION system delivers more than 2000 mL (insulin and dextrose infusions) during the 24-hour closed loop glucose control session in two subjects. 6. The FUSION system experiences any unanticipated adverse device effect (UADE). 7. The study's principal investigator determines that the safety of the studies subjects is being compromised through use of the FUSION system.

15.	**Obtain Reference Glucose Values using the Nova StatStrip Hospital Glucose Meter System every 10-60 minutes from time 4 to 32 hours according to the following guidelines:** **A. Every 10 minutes:** Monitor the subject's Reference Glucose Values every 10 minutes whenever either of the following occur: I. Either of the Dexcom G6 CGM's is less than 70 mg/dL. II. When the most recent Reference Glucose Value is less than 70 mg/dL. Discontinue every 10 minute Reference Glucose Value monitoring when <u>both</u> of the following have occurred: I. Both Dexcom G6 CGM's are greater than 70 mg/dL. II. The subjects have two consecutive Reference Glucose Values greater than 70 mg/dL. These Reference Glucose Values will be measured by the Nova StatStrip Hospital Glucose Meter System on either a venous or capillary blood sample. **B. Every 30 minutes:** Monitor the subject's Reference Glucose Values every 30 minutes when the following occur: I. After both Dexcom G6 CGM's begin to return glucose readings after their original insertion and prior to the onset of the closed loop glucose control session, for purposes of verifying the accuracy of the CGM's. This monitoring prior to the onset of the closed loop glucose control session may be discontinued once both CGM's have met the following <u>CGM Validation Criteria</u> on two consecutive Reference Glucose Values: CGM readings must be within ± 20 mg/dL of the Reference Glucose Value for CGM readings < 100 mg/dL or CGM readings must be within ± 20% of Reference Glucose Values for CGM readings >= 100 mg/dL on two consecutive Reference Glucose Values. II. During the first 2 hours of the closed loop glucose control session (time 5-7 hours). III. When either Dexcom G6 CGM has a glucose reading less than 85 mg/dL displayed on either the Dexcom G6 Receiver of the Dexcom G6 Follow App. IV. During periods of severe hyperglycemia, which is defined as a CGM or Reference Glucose Value greater than 240 mg/dL. V. When only one Dexcom G6 CGM is available for use by the FUSION system for glucose control. VI. After a CGM has been replaced, and until the replaced CGM has met the above noted <u>CGM Validation Criteria</u>. VII. When the subject experiences any signs of neuroglycopenia, regardless of the glucose level displayed by the CGM's. VIII. From time 29-32 hours, which is the 3 hour time period after conclusion of the closed loop glucose control session.

	C. Every 60 minutes: Monitor the subject's Reference Glucose Value every 60 minutes when the following occur: i. During the last 22 hours of the closed loop glucose control session (time 7-29 hours), if the following occur: a) Both CGM's are in the range of 85-240 mg/dL and the subject is not experiencing any signs of neuroglycopenia. Result: _____ mg/dL, Time: _____ (24 hour clock) **Note:** Notify study team if the CGM or Reference Glucose Value is < 70 mg/dl or > 300 mg/dl.
16.	**Dexcom G6 CGM Placement, Calibration and Replacement** **Visit 3 (Time 0 to 5 hours):** Place two Dexcom G6 CGM's in the abdomen 5 cm to the right and left of the umbilicus (Figure 28).  ***Figure 28 – Green shaded areas denote appropriate areas of the abdominal wall to place the Dexcom G6 CGM's. This figure is from the Dexcom G6 CGM user manual.***

Make sure the Dexcom G6 Transmitters are labeled "#1" and "#2". These labels should be in a clearly visible position after the Transmitters have been attached to the Dexcom G6 glucose sensors. Once both Dexcom CGM's begin to return glucose values, obtain a Reference Glucose Value using the Nova StatStrip Hospital Glucose Meter System. If either of the Dexcom CGM's do not meet CGM Validation Criteria, they may be calibrated. The Dexcom G6 CGM's must meet the following CGM Validation Criteria throughout the CRC study session (visit 3), otherwise they will be calibrated as often as is necessary:

1. CGM readings must be within ± 20 mg/dL of the Reference Glucose Value for CGM readings < 100 mg/dL or CGM readings must be within ± 20% of Reference Glucose Values for CGM readings >= 100 mg/dL on two consecutive Reference Glucose Values.

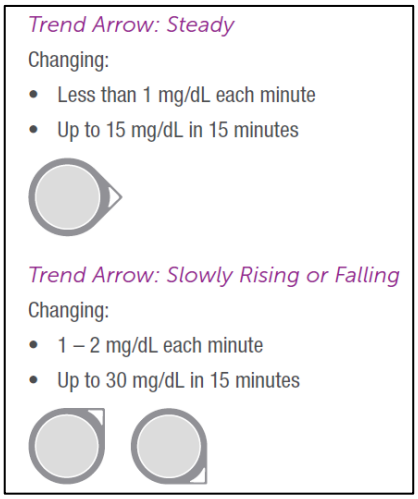


Figure 29 – Glucose rate of change, as noted by the Dexcom G6 CGM trend arrows.

Calibrations should only be attempted when the glucose rate of change is less than ± 2 mg/dL/min on the Dexcom G6 CGM (see figure 29).

If after two calibration attempts prior to beginning the closed loop glucose control session (time 0-5 hours) the CGM(s) still do not meet CGM Validation Criteria, they may be replaced. The closed loop glucose control session may not begin until there are two working Dexcom G6 CGM's in place, and both CGM's have met the above noted CGM Validation Criteria.

Closed Loop Glucose Control Session (Time 5 to 29 hours):

Inspect the CGM sites (see Monitoring Activities) and ensure proper performance and communication to the two Dexcom G6 Receivers that are labeled "#1" and "#2", and that are part of the FUSION system (Figure 20); ensure communication with the Dexcom G6 Follow APP on the two mobile phones labeled "#1" and "#2". The CGM's may be replaced during the closed loop glucose control session for any of the following reasons:

1. The CGM(s) do not meet the above noted CGM Validation Criteria and are unable to be calibrated after two attempts over a two-hour period of time.
2. If the CGM measurement is > 180 mg/dL and the simultaneous (e.g., within 5 minutes) Reference Glucose Value is < 100 mg/dL, the CGM may be replaced as this scenario may lead to inadvertent insulin administration by the FUSION system, which may result in hypoglycemia (< 70 mg/dL).
3. If the CGM measurement is < 100 mg/dL and the simultaneous (e.g., within 5 minutes) Reference Glucose Value is > 180 mg/dL, the CGM may be replaced as this scenario may lead to a delay in the treatment of hyperglycemia, which will increase the risk for DKA in type I diabetic subjects.

	4. The CGM(s) experience repeated compression artifact that is unable to be relieved through repositioning of the subject. Compression artifact is a sudden non-physiologic fall in one of the CGM glucose levels (e.g., < ± 2 mg/dL/min), when the second CGM does not experience this same degree of fall in its glucose level. The FUSION system monitors for compression artifact and will display an alarm alerting the clinical study nurse of its occurrence, and the need to reposition the subject so that they are not directly laying on the transmitter/sensor pair. 5. The subject is experiencing significant bleeding, pain, or signs of infection at the CGM insertion site. 6. The CGM transmitter/sensor pair stops working for any reason. If the Dexcom G6 CGM's need to be replaced during visit 3, the preferred replacement site is another abdominal position (see Figure 28). If another abdominal site is used, place the new CGM at least 10 cm away from the other abdominal CGM that is still working properly. As an alternative, and only if another abdominal site is not available or may result in further compression artifacts, a replacement CGM may be placed in the posterior upper arm position, on the contralateral side from the remaining CGM (e.g., if remaining CGM is on the right side of the abdomen, place the replacement CGM on the posterior aspect of the left upper arm). In the event a replacement CGM is used, it must be calibrated until it meets the above noted CGM Validation Criteria. The position of the CGM's and all calibration attempts will be noted on the Case Report Form.
17.	**Frequency of CGM Calibration** The CGM's may be recalibrated as often as necessary during the closed loop glucose control session (time 5-29 hours) if they do not meet the following CGM Validation Criteria: 1. CGM's glucose readings must be within ± 20 mg/dL of Reference Glucose Values for CGM readings less than 100 mg/dL or must be within ± 20% of Reference Glucose Values for CGM readings greater than 100 mg/dL. Only CGM's not meeting the above noted CGM Validation Criteria will be calibrated, thus either one or both CGM's may be calibrated at any point in time, depending on the circumstances. In addition, the FUSION system monitors the CGM's for signs of significant deviation (e.g., > 20%) from the average glucose value used by the FUSION system for glucose control. If the FUSION system detects CGM deviation of > 20% from the average glucose value used by the FUSION system (e.g., CGM #1 = 70 mg/dL, CGM #2 = 130 mg/dL, and average glucose value used by the FUSION system = 100 mg/dL) it will display an alarm alerting the clinical study nurse of this occurrence, and request that both CGM's be recalibrated against a Reference Glucose Value. To be clear, if the CGM's meet the above noted CGM Validation Criteria throughout their time of use in visit 3, and the FUSION system does not automatically call for a CGM calibration, it is possible to complete visit 3 with no calibration of either CGM.

18.	**Standard Blood Collection Protocol per CRC guidelines** **RN:** Draw blood glucose sample from retrograde intravenous line: Draw 0.5 mL of whole blood to measure glucose levels using the Nova StatStrip Hospital Glucose Meter System every 10-60 minutes (time 4 to 32 hours).
19.	**Meal Challenge Protocol** Time 5 hours (~1200 on day 1): Subject to consume lunch with 60 grams of carbohydrate. Time 11 hours (~ 1800 on day 1): Subject to consume dinner with 75 grams of carbohydrate. Time 25 hours (~0800 on day 2): Subject to consume breakfast with 50 grams of carbohydrate. Carbohydrates should make up 45-60% of the total Kcal's of each meal. Time 5 to 29 hours: Closed loop control of blood glucose with FUSION system (Figure 20), to control range of 100-140 mg/dL. Throughout the entirety of the subjects stay in the CRC (e.g., time 0 to 32 hours), if the subject has a Reference Glucose Value less than 70 mg/dL or is experiencing signs of neuroglycopenia (hypoglycemia of sufficient duration and degree to interfere with normal brain metabolism and function) at any Reference Glucose Value, they will be offered snacks and/or glucose containing juice.
20.	**RECOVERY PERIOD (Time 29 to 32 hours)** **1. Type 1 Diabetic Subjects:** Type 1 diabetic subjects will be required to have four consecutive Reference Glucose Values within the range of 80-250 mg/dL, with the most recent rate of change being less than ± 2 mg/dL/min, which is equal to either a single sideways arrow or a single up or down arrow as noted in the illustration above (Figure 29), which was taken from Dexcom G6 CGM manual. The glucose sample source can be either from a venous catheter sample, or from a capillary fingerstick. The Nova StatStrip Hospital Glucose Meter System will be used to analyze the sample for glucose. Following standard practice, subjects with type 1 diabetes will receive a dose of basal insulin dose two hours before discontinuation of the FUSION systems continuous insulin infusion (CII), as it is expected that basal insulin levels will slowly reach a therapeutic level after administration. An endocrinologist (Dr. Pasquel or Dr. Davis) will determine the dose of the basal insulin before CII discontinuation for subjects with type 1 diabetes. The next dose of basal insulin (at home) and transition to the participants home regimen will be determined by Dr. Pasquel or Dr. Davis.

The study's principal investigators (Dr. Pasquel or Dr. Davis) will determine the short acting insulin dose to cover the lunch (60 grams of carbs) that is consumed at approximately 1200 hours on Day 2, based on the participant's medical history, pre-prandial Reference Glucose Value that is measured by the Nova StatStrip Hospital Glucose Meter System, and carbohydrate load in the meal.

Subjects using insulin pumps will start continuous subcutaneous insulin therapy with rapid acting insulin immediately after stopping the FUSION systems CII. Dr. Pasquel or Dr. Davis may adjust the settings of the subject's insulin pump prior to discharge from the CRC to minimize the risk of hypoglycemia or DKA.

2. Type 2 Diabetic Subjects:

Type 2 diabetic subjects will be required to have four consecutive Reference Glucose Values within the range of 80-250 mg/dL, with the most recent rate of change being less than ± 2 mg/dL/min, which is equal to either a single sideways arrow or a single up or down arrow as noted in the above illustration (Figure 29).

The glucose sample source can be either from a venous catheter sample, or from a capillary fingerstick. The Nova StatStrip Hospital Glucose Meter System will be used to analyze the sample for glucose.

Recovery Period (Time 29 to 32 hours) – Subject to resume subcutaneous insulin injections:

i. Subjects routinely injecting long acting insulin only in the morning will take a dose of long acting insulin at 2/3 of their normal dose. ___ units given at __ __ : __ __ (24 hour clock).

   i. Subjects routinely injecting long acting insulin morning and evening will take a dose of long acting insulin at ½ their normal morning dose and be instructed to take their evening dose as usual. ___ units given at __ __:__ __ (24 hour clock).

   ii. Subjects routinely injecting long acting insulin only in the evening will take a dose of long acting insulin at 1/3 of their normal dose and be instructed to take their evening dose as usual.

___ units given at __ __:__ __ (24 hour clock).

   iii. The study's principal investigators (Dr. Pasquel or Dr. Davis) will determine the short acting insulin dose to cover the lunch (60 grams of carbs) that is consumed at approximately 1200 hours on Day 2, based on the participant's medical history, pre-prandial Reference Glucose Value that is measured by the Nova StatStrip Hospital Glucose Meter System, and carbohydrate load in the meal.

	Both type 1 and type 2 diabetic subjects will consume a lunch consisting of 60 grams of carbohydrates beginning at 1200 hours on day 2. The study nurse will check Reference Glucose Values every 30 minutes with the Nova StatStrip Hospital Glucose Meter System – Times 29, 29.5, 30, 30.5, 31, 31.5, and 32 hours, etc., until the subjects Reference Glucose Values are in the range of 80-250 mg/dL for a period of at least two hours after the completion of the closed loop glucose control session, and the most recent glucose rate of change is less than ± 2 mg/dL/min. If the subject is removed from the study early due to the presence of hypoglycemia (e.g., < 54 mg/dL or < 70 mg/dL with neuroglycopenic symptoms) or for any other reason, they will have ongoing monitoring in the CRC until they have had glucose values in the range of 80-250 mg/dL for a period of at least two hours, and until their most recent glucose rate of change is less than ± 2 mg/dL/min. In the event the subject is removed from the study early, any short or long acting insulin dosing needed from the time the subject is removed from the study until the time the subject is discharged from the CRC, will be per the orders of the study's principal investigators (Dr. Pasquel or Dr. Davis). If the subjects CGM or Reference Glucose Values are less than 70 mg/dL at the time they are removed from the study, they will have Reference Glucose Values measured every 10 minutes until such time as their glucose values are greater than 70 mg/dL. If the subject develops signs of diabetic ketoacidosis (e.g., Reference Glucose Value > 240 mg/dL and blood ketones > 1 mmol/L), they will have a basic metabolic panel, venous pH, and beta hydroxybutyrate drawn. If the subject develops diabetic ketoacidosis, they will be stabilized and have ongoing care per the usual routine of Emory Healthcare.
21.	**Intravenous Catheter Removal:** Remove both IV catheters once the subjects Reference Glucose Value is in the range of 80-250 mg/dL for a period of at least two hours after the completion of the closed loop glucose control session, and when the most recent glucose rate of change is less than ± 2 mg/dL/min. This criterion will not be met prior to time 32 hours (~ 1500 hours of 2nd day in the CRC). The subject may be discharged from the CRC unit once this criterion has been met.
22.	**Discharge Criteria** **The subjects Reference Glucose Value must be between 80-250 mg/dL for a period of 2 hours before discharge, and their most recent glucose rate of change must be less than ± 2 mg/dL/min. For subjects who have been placed back on their usual continuous subcutaneous insulin infusion pump, they may be discharged once their Reference Glucose Value is between 80-250 mg/dL for a period of 2 hours, and their most recent glucose rate of change must be less than ± 2 mg/dL/min.**

	All subjects must be observed for a minimum of 3 hours after the conclusion of the closed loop glucose control session and for at least 60 minutes after their most recent subcutaneous insulin injection (subjects on MDI insulin therapy), before being discharged from the CRC. **End of Study Reference Glucose Value,** BG: ____ mg/dL, Time: _____ (24 hour clock)
23.	After the subjects have been discharged from the CRC, they will be instructed to check their blood glucose levels at home using their blood glucose meter at the following times: 1. On arrival at home. 2. Before dinner. 3. At 9 P.M. 4. On awakening the next morning. Subject to call study coordinator with concerns they have about their glucose levels or any other issue.

Attachment 1

Serious Adverse Event Report Form

IMT2022-1-A1

Serious Adverse Event

An adverse event is any untoward medical event associated with use of a drug or drug delivery system in humans, whether or not it is considered related to a drug or drug delivery system. For purposes of this study, a Serious Adverse Event (SAE) is any adverse event from this study that results in one of the following outcomes:

- Death
- A life threatening experience
- Persistent or significant disability/incapacity
- Seizure secondary to hypoglycemia
- Myocardial infarction that is temporally related to a hypoglycemic (<70 mg/dL) event
- Cardiac dysrhythmia that that is temporally related to a hypoglycemic (<70 mg/dL) event
- Any other complication related to hypoglycemia
- Reference Glucose Value less than 54 mg/dL
- Considered significant for any other reason

Serious Adverse Event (SAE) Report Form

DEMONSTRATION OF AN ARTIFICIAL INTELLIGENCE BASED CLOSED LOOP GLUCOSE CONTROL SYSTEM AS A THERAPEUTIC MODALITY IN TYPE 1 AND TYPE 2 DIABETIC PATIENTS

Protocol Number: IMT2022-1
Site: _____
Pt ID: _____

1. SAE Onset Date: _____ (dd/mm/yyyy)

2. SAE Stop Date: _____(dd/mm/yyyy)

3. Location of serious adverse event: _____

4. Was this an unexpected adverse event? Yes No

5. Brief description of participant(s) with no personal identifiers:
   Sex: F M Age: _____

   Diagnosis for study participation: _____

6. Brief description of the nature of the serious adverse event (attach description if more space needed):
   _____
   _____

7. Category of the serious adverse event:
   - Death – date __/___/___ (dd/mm/yyyy)

- Complication from severe hypoglycemia
- Life-threatening
- Hospitalization- prolonged
- Disability / incapacity
- Required intervention to prevent permanent impairment

Other:_____

8. Intervention type:

Medication or Nutritional Supplement: specify_____

Device: Specify: _____

Surgery: Specify: _____

Behavioral/Life Style: Specify: _____

9. Relationship of event to intervention:

- **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.

10. Was study intervention discontinued due to event? Yes No

11. What medications or other steps were taken to treat serious adverse event?

12. List any relevant tests, laboratory data, history, including preexisting medical conditions

13. Type of report:

Initial

Follow-up

Final

Signature of Principal Investigator: _____ Date: _____