Protocol

Title: Automated Insulin Delivery for INpatients with DysGlycemia (AIDING) Feasibility Study

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Signature Page

Automated Insulin Delivery for INpatients with DysGlycemia (AIDING) Feasibility Study

IDE Sponsor: Francisco J. Pasquel, MD, MPH

Version Number: 2.2

23 NOV 2020

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Automated Insulin Delivery for INpatients with DysGlycemia (AIDING) Feasibility Study

IDE Sponsor: Francisco J Pasquel, MD, MPH

Funded by: Insulet Corporation

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23 NOV 2020

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The primary purpose of this pilot study is to assess the feasibility HCL use in the inpatient setting; therefore, no formal power calculations were performed. The main objectives of this study are to improve the quality and efficiency of the main study. In addition, it is conducted in order increase the investigators' experience with the technology in a different setting. We will list values for each patient as well as provide summary statistics appropriate to the distribution. To determine the operability of AID in the hospital (Aim 1) we will calculate the proportion of time spent in HCL after CGM sensor values meet validation criteria [sensor glucose values are within ±20% of POC values for glucose levels ≥70 mg/dL or ±20 mg/dL for POC glucose values <70 mg/dL]. To evaluate glycemic control (Aim 2) we will determine the percentage of time sensor glucose values are within target glucose range [time-in-range (TIR); 70-180 mg/dL], during closed-loop insulin delivery. 54

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACE	Alternate Controller Enabled
ADE	Adverse Device Effect
AE	Adverse Event
AID	Automated Insulin Delivery
ARD	Absolute Relative Difference
BG	Blood Glucose
BMI	Body Mass Index
CEG	Clarke Error Grid
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
COVID-19	Coronavirus-2019
CRF	Case Report Form
CRP	C-Reactive Protein
CV	Coefficient of Variation
DIC	Disseminated Intravascular Coagulation
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
EGV	Estimated Glucose Value
EHR	Electronic Health Record
EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GV	Glycemic Variability
HbA1c	Hemoglobin A1c
HCW	Healthcare Worker
HDP	Horizon Data Portal
ICR	Insulin-to-Carbohydrate Ratio
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IL-6	Interleukin-6
IRB	Institutional Review Board
ISF	Insulin Sensitivity Factor
IV	Intravenous
MARD	Mean Absolute Relative Difference
MPC	Model Predictive Control
PDM	Personal Diabetes Manager
POC	Point-of-Care
PPE	Personal Protective Equipment
PUI	Person Under Investigation
QA	Quality Assurance
QC	Quality Control

ABBREVIATION	DEFINITION
RBM	Risk-Based Monitoring
RCT	Randomized Controlled/Clinical Trial
SAE	Severe Adverse Event
SD	Standard Deviation
T1	Type 1
T2	Type 2
TAR	Time Above Range
TBI	Total Basal Insulin
TBR	Time Below Range
TDD	Total Daily Dose
TDI	Total Daily Insulin
TIR	Time In Range
UADE	Unanticipated Adverse Device Effect

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: **Automated Insulin Delivery for Inpatients with Dysglycemia (AIDING) Feasibility Study**

Protocol Version/Date: **v. 2.2 / 11/23/2020**

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Sponsor with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following (use applicable regulations depending on study location and sponsor requirements; examples follow): United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

For the foreign sites, the trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP), the Declaration of Helsinki, and specific regulations applicable to the countries in which the trial will be conducted.

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____   Date: _____ / _____ / _____

                                                                             dd   mmm   yyyy

Investigator's Name: _____

Site Name/Number: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Automated Insulin Delivery for Inpatients with Dysglycemia (AIDING) Feasibility Study
Précis	This single-arm stepwise feasibility study will test initial deployment of hybrid closed-loop (HCL) automated insulin delivery (AID) using the Omnipod 5/Horizon HCL system with remote monitoring and device operation capabilities to hospitalized patients admitted to the general medical/surgical floorwith diabetes (type 1 or type 2) requiring insulin therapy. All enrolled participants will be placed on HCL insulin therapy for 10 days or until hospital discharge (if less than 10 days) to determine functional operability of the system and its effect on glycemic control in the hospital setting. This study will generate preliminary data to inform the design of a large multi-institution randomized controlled trial to assess superiority of HCL compared to standard inpatient insulin therapy.
Investigational Device	The Omnipod 5/Horizon HCL system, consists of a disposable insulin infusion pump (or "pod"), a built-in model predictive control (MPC) insulin dosing algorithm, and a remote Personal Diabetes Manager (PDM) interface, that interact with a Dexcom G6 continuous glucose monitor (CGM) to automatically control insulin delivery based upon real-time glucose values. The PDM component also enables remote interaction with the system, including glucose monitoring as well as insulin dosing management and adjustments.
Objectives	Primary objective:
	To investigate functional operability and implementation of the Omnipod 5/Horizon HCL system in the hospital setting.
	Secondary objectives:
	To describe glycemic control, device settings and insulin delivery parameters, and explore staff and patient perceptions associated with early use of the Omnipod 5/Horizon HCL system in the hospital setting.
Study Design	Pilot and Feasibility
Number of Sites	3
Endpoint	**Primary Endpoints:**
	Aim 1 (Operability): Proportion of time spent in HCL after CGM sensor meets initial validation criteria [sensor glucose value is within ±20% of POC values (for glucose levels ≥70 mg/dL) or ±20 mg/dL for POC glucose values <70 mg/dL].
	Aim 2 (Glycemic control): Percentage of time sensor glucose is within target glucose range [time-in-range (TIR)], defined as 70-180 mg/dL.
	Key Secondary Endpoints:
	Aim 1.1 Operability (System function):

PARTICIPANT AREA	DESCRIPTION
	- Time from enrollment to start of HCL therapy (after initial CGM validation) - Percentage of time with CGM readings - Percentage of CGM values meeting accuracy criteria for bolus/correction insulin dosing - Number of CGM readings within %15/15 of POC readings and within %20/20 of POC readings with the cut point at 70 mg/dL *Aim 1.2 Perception (qualitative analyses):* - Patient and Providers: Open-ended feedback - Patient and Providers: Survey questionnaire results *Aim 2.1. Glycemic control:* - Number of hypoglycemic (<70 mg/dL) and clinically important hypoglycemic (<54 mg/dL) episodes per patient and per patient-day - Percent time below range (TBR, <70mg/dL) - Percent time below range (<54 mg/dL) - Percent time above range (TAR, >180 mg/dL) - Percent time in severe hyperglycemia (>250 mg/dL) - Coefficient of variation (CV), standard deviation (SD) *Aim 2.2 HCL Settings:* - Frequency of setting adjustments for clinically-important hypoglycemia (<54 mg/dL): Overall, to basal rate, to insulin carb ratio (ICR), to insulin sensitivity factor (ISF) - Frequency of setting adjustments for prolonged hyperglycemia (>250 mg/dL for >1 hour): Overall, to basal rate, to ICR, to ISF - Insulin requirements: Total daily insulin (TDI), Total daily basal insulin (TBI), Total daily bolus (meal and correction). **Key Safety Outcomes:** - Reportable hypoglycemia: defined as an event that required assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that the participant was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. - Diabetic ketoacidosis
Population	**Key Inclusion Criteria:**

PARTICIPANT AREA	DESCRIPTION
	- Patients ≥18 years of age with insulin-treated T1 or T2DM admitted to general (non-intensive care) medical-surgical hospital service requiring inpatient insulin therapy. **Key Exclusion Criteria:** - Patients admitted the ICU or anticipated to require ICU transfer - Anticipated length of hospital stay <48 hours. - Evidence of hyperglycemic crises (diabetic ketoacidosis or hyperosmolar hyperglycemic state) at enrollment - Severely impaired renal function (eGFR < 30 ml/min/1.73m^2) or clinically significant liver failure - Severe anemia with hemoglobin <7 g/dL - Evidence of hemodynamic instability - Hypoxia (SpO2 <95% on supplemental oxygen) - Pre-admission or inpatient total daily insulin dose >100 units - Mental condition rendering the participant unable to consent or answer questionnaires - Pregnant or breast-feeding at time of enrollment - Unable or unwilling to use rapid-acting insulin analogs (Humalog, Admelog, Novolog or Apidra) during the study - Use of hydroxyurea or high-dose ascorbic acid (>1g/day) - COVID-19 infection or person under investigation (PUI) on isolation precautions
Sample Size	18 patients
Phase	Pilot, Feasibility
Treatment Groups	All enrolled participants will be placed on HCL insulin therapy for up to 10 days or until hospital discharge.
Participant Duration	Up to 10 days during inpatient stay

OVERVIEW OF STUDY DESIGN

This multicenter study testing the feasibility of AID (Omnipod 5/Horizon HCL system) in the hospital will be conducted across three sites [Emory, Stanford, University of Virginia (UVA)]. To ensure safety of participants with this new impatient glycemic control approach we will employ a stepwise enrollment plan with two phases (**Figure 1**). We will enroll patients ≥18 years of age with insulin-treated type 1 (T1) or type 2 (T2) DM requiring insulin therapy during hospitalization admitted to the general medical/surgical floor (non-ICU). To have 9 subjects in each phase cohort who have used the system for at least 48 hours, we will enroll up to a total of 30 participants. All participants will be placed on AID for inpatient glucose management.

The first phase of the study will combine automated insulin delivery (AID) with intensified POC glucose monitoring (minimum of 6 POC glucose tests per day; n=9 subjects). During phase 2, AID will continue with less frequent POC glucose monitoring (approximately 4 times per day, standard-of-care; n=9 subjects) (**Figure 1**). IRB-approved informed consent will be obtained by study personnel designated at each site. Exclusion criteria include: **1)** patients requiring total daily insulin dose >100 units, **2)** patients admitted to ICU, **3)** patients anticipated to require <48 hours of admission, **4)** patients with evidence of hyperglycemic crises (diabetic ketoacidosis or hyperosmolar hyperglycemic state), **5)** patients with severely impaired renal function (eGFR < 30 ml/min/1.73m^2), **6)** clinically significant liver failure, **7)** severe anemia (hemoglobin <7 g/dL), **8)** hypoxia (SpO2 <95% on supplemental oxygen), **9)** evidence of hemodynamic instability, **10)** active or suspected COVID-19 infection, **11)** a mental condition rendering the participant unable to consent or answer questionnaires, **12)** pregnancy or breast feeding at time of enrollment, or **13)** use of hydroxyurea or high-dose ascorbic acid.
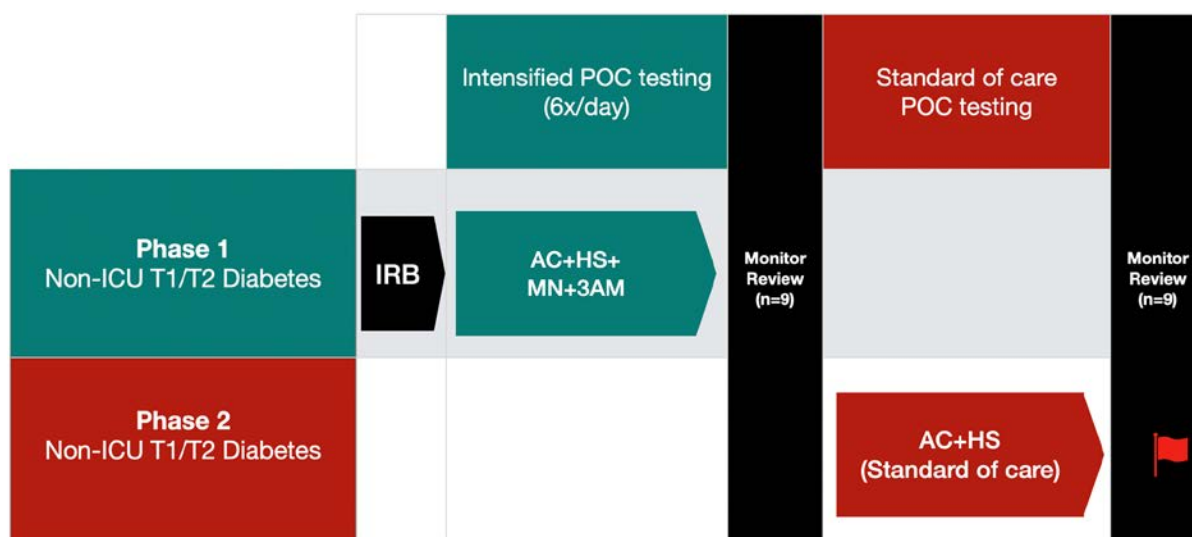
Figure 1. AIDING Feasibility Study Stepwise Enrollment Design. IRB: Institutional Review Board; POC: point-of-care testing; AC: Before meals; HS: bedtime; MN: midnight.

1 # Chapter 1: Background Information

2 **1.1 Introduction**

3 The purpose of this study is to assess the safety and efficacy of using the Omnipod 5/Horizon
4 automated insulin delivery (AID) system in improving glycemic control for hospitalized patients
5 requiring subcutaneous insulin therapy. This is the first automated insulin delivery system which
6 is well-suited for the hospital environment given its remote management capabilities with
7 disposable components.

8 The coronavirus disease 2019 (COVID-19) pandemic has highlighted how accelerated use of
9 technologies [e.g., telemedicine, e-consults, and remote monitoring] has helped healthcare
10 systems adapt care delivery while minimizing exposure risk. The pandemic has also shed light
11 on the bedside care burden associated with inpatient diabetes management in its current state. As
12 more patients are admitted with COVID-19 infection, there is continued concern surrounding
13 resource limitations, including PPE. These concerns have led to transformations in clinical care
14 that focus on the preservation of scarce resources while continuing to provide the highest level of
15 clinical care. Inpatient diabetes (DM) management is one realm of clinical care that has seen
16 major changes in the setting of COVID-19, mostly due to the time- and labor-intensive efforts
17 required to care for hospitalized patients with DM.[1] In the United States, it is estimated that
18 about one in five patients with COVID-19 admitted to the hospital has DM.[2] The increasing
19 proportion of hospitalized patients with DM and concurrent COVID-19 infection continues to
20 highlight the importance of advancing inpatient diabetes care to balance the competing demands
21 of frequent glucose monitoring and timely insulin administration with the bedside contact
22 required for these efforts when PPE is scarce.

23 In Atlanta, a diagnosis of diabetes is associated with a threefold increase in the odds of
24 hospitalizations.[3] Among those patients with COVID-19 hospitalized in Georgia (primarily
25 metropolitan Atlanta) beginning in February, DM was documented in 39.7% of hospitalized with
26 COVID-19,[4] and a recent report showed about 46% of critically ill patients had DM in COVID
27 units in the Emory healthcare system.[5] Over 3500 cases of COVID-19 have been documented at
28 Emory until the end of July 2020, including 883 patients with diabetes, of whom 114 expired
29 (14%). At Stanford, of 2345 patients hospitalized with COVID-19 from March 1 to June 30,
30 2020, 25% (580) had diabetes. Among these 19% were intubated, and 2.6% of these patients
31 died. At UVA, a sample of 141 patients hospitalized with COVID-19 showed 52% required
32 treatment with insulin. We estimate at least 30% of patients with COVID-19 will have DM at
33 the three centers.

34 The use of AID systems continues to grow in the outpatient setting among patients with both
35 type 1 and type 2 diabetes. Preliminary data from AID trials with a single non-commercial
36 European system (using an insulin pump with tubing) has shown significant improvements in
37 glycemic control in diverse populations, without increasing the risk of hypoglycemia.[6-8] There is,
38 however, no clinical trial data with the use of AID in the hospital in the US.

39 The AID system consists of the Omnipod 5/Horizon insulin infusion pump or "pod," the Horizon
40 Personal Diabetes Manager (PDM) and a Dexcom G6 CGM **(Figure 2)**. The system's
41 embedded model predictive control (MPC) algorithm utilizes CGM glucose values, rate of
42 glucose change, and active insulin from previous boluses to make insulin dosing decisions. The
43 algorithm has been tested in hundreds of patients ranging in age from 2 to 70 years old and has

44 been stress tested with missed insulin boluses for
45 meals, exercise, and insulin over-boluses for
46 meals **(Table 1)**. The pod holds 200 units of
47 insulin, the embedded algorithm, and directly
48 receives Bluetooth glucose values from the G6
49 sensor. The pod is worn for three days and then
50 disposed, thereby eliminating the possibility of
51 cross-contamination between patients. The G6
52 CGM sensor lasts 10 days, while its transmitter
53 lasts 3 months. Neither CGM component (sensor
54 or transmitter) will be reused between patients.
55 The system uses a dedicated smartphone
56 [Horizon Personal Diabetes Manager (PDM)] to
57 allow remote monitoring (via cellular data and
58 WiFi networks). Insulin boluses and adjustments
59 to pump settings can be made from the
60 smartphone if it is within Bluetooth distance of
61 the pod (about 20-30 feet). We have tested this

Figure 2. Omnipod5/Horizon AID system.

62 communication within the hospital setting and it has worked well, allowing remote bolusing and
63 monitoring from outside of a patient's room (see preliminary data).

64 **1.2 Rationale**

65 **1.2.1 Inpatient diabetes management and glycemic control targets**

66 In the Leuven Surgical Trial, Van den Berghe et al. reported improvement in mortality and
67 morbidity in adult ICU patients using a glucose target of 80-110 mg/dL.[9-12] This mobilized a
68 drive to significantly reduce inpatient glucose levels. However, NICE-SUGAR, a large
69 multicenter randomized controlled trial aiming to reproduce those findings, instead showed an
70 increase in 90-day mortality in the intensive management group targeting euglycemia.[13] These
71 results were later attributed to an increased rate of moderate to severe hypoglycemia seen among
72 the group with more intensive glycemic targets (81-108 mg/dL).[14] Subsequently, to balance the
73 important benefits of treating hyperglycemia against the increased risk of hypoglycemia in
74 hospitalized patients, the American Diabetes Association (ADA) and American Association of
75 Clinical Endocrinologists (AACE) recommended an inpatient target glucose range of 140-180
76 mg/dL. Similarly, the Society of Critical Care Medicine (SCCM) and the European Society of
77 Intensive Care Medicine (ESICM) have also adopted a glucose goal ≤180 mg/dL in their
78 collaborative Surviving Sepsis Campaign guidelines on the management of sepsis and septic
79 shock. While these parameters provide the current standard directing inpatient glucose
80 management, glycemic variability (GV) has also generated interest since several studies have
81 shown an increased risk of mortality independent of mean glucose levels associated with
82 increased GV.[15-17]

83   Consideration has been made as to whether strict glucose control can improve outcomes
84   specifically in hospitalized patients with COVID-19. A multi-center retrospective analysis of
85   7,337 patients with COVID-19 in Hubei Province, China[18] reported an increased incidence of
86   acute respiratory distress syndrome (ARDS), acute kidney injury, acute cardiac injury,
87   disseminated intravascular coagulation (DIC), and all-cause in-hospital mortality among patients
88   with pre-existing DM. As expected, these patients also had higher levels of acute inflammatory
89   markers [C-reactive protein (CRP), procalcitonin, and D-dimer]. Yet, a sub-analysis of the cohort
90   with DM revealed that in those with well-controlled glucose values (70-180 mg/dL), these
91   endpoints and laboratory findings were all significantly reduced.[18] Similar findings were also
92   reported by Sardu et al.[19] in a 28-day prospective study to assess the effect of intensive glycemic
93   control on progression to severe COVID-19 disease (ICU admission, mechanical ventilation, or
94   death). In this study of 59 patients admitted with moderate COVID-19 pneumonia, two
95   subgroups were characterized based on the admission glucose >140 mg/dL (hyperglycemic), or
96   <140 mg/dL. Of the hyperglycemic patients, 72% had a diagnosis of DM prior to admission. All
97   25 patients with hyperglycemia were asked to consent to intravenous (IV) insulin infusion if their
98   glucose exceeded 180 mg/dL. Fifteen patients consented and were given IV insulin to target a
99   glucose of 140-180 mg/dL, while the other 10 patients received standard basal-bolus
100   subcutaneous insulin injections. The mean glucose during hospitalization for those receiving IV
101   insulin therapy was 138 ± 33 mg/dL, and 192 ± 15 mg/dL for those not receiving IV insulin.
102   Hyperglycemia and higher baseline levels of interleukin 6 (IL-6) and D-dimer were associated
103   with progression to severe disease. However, of those who opted for IV insulin, only 33%
104   progressed to severe disease, compared to 80% of those who did not. Additionally, those
105   receiving IV insulin demonstrated much larger reductions in IL-6 and D-dimer levels at one- and
106   two-week time points. These early studies suggest that improved glucose control may promote
107   better clinical outcomes among patients with COVID-19.

108   However, use of continuous IV insulin infusion requires hourly interventions and significant
109   oversight by healthcare providers. In non-ICU patients, basal-bolus insulin regimens continue to
110   be the mainstay of therapy for patients with hyperglycemia in the hospital, relying heavily on the
111   ability of healthcare workers (HCW) to perform frequent blood glucose monitoring and timely
112   administration of multiple insulin injections to achieve glycemic control.[20] During COVID-19,
113   related shortages in PPE and the healthcare workforce will undoubtedly have a negative impact
114   on inpatient glycemic control and outcomes for these patients. Additionally, inpatient
115   hyperglycemia itself may become increasingly challenging to mitigate, as rapidly evolving data
116   has directed attention towards the use of high-dose steroids in the treatment of COVID-19.[21]
117   Recent preliminary results from the "Randomised Evaluation of COVID-19 Therapy"
118   (RECOVERY) trial showed a significant reduction in 28-day mortality among patients requiring
119   supplemental oxygen (including non-invasive ventilation) or invasive mechanical ventilation
120   treated with high-dose dexamethasone (6 mg daily).[22] Therefore, in light of the baseline
121   prevalence and prognostic implications of pre-existing DM, early reports suggesting an
122   association between glucose control and improved outcomes, and the now probable forthcoming
123   increase in steroid usage among patients with COVID-19, maintaining glycemic control has
124   become an integral part of inpatient COVID-19 management.

125   Advances in diabetes technology have changed the face of diabetes care in the outpatient setting
126   through the use of CGM, insulin pump therapy and the integration of these two technologies to

127 provide AID.[23] Recent efforts have focused on moving these technologies to the inpatient setting
128 to improve hospital diabetes management.[24] Our interest in this concept predates the pandemic,
129 and we have previously reported our experience using CGM in the inpatient setting, including
130 the implementation of a glucose telemetry system (NCT03877068).[25-28] Recently, this progress
131 has been accelerated and has become available for more widespread clinical implementation
132 during the COVID-19 pandemic. During the beginning of the pandemic, the US Food and Drug
133 Administration (FDA) allowed for the use of CGM in the inpatient setting, with many hospitals
134 rapidly implementing CGM with little guidance in a desperate effort to preserve PPE and glucose
135 monitoring abillities.[25,29] Already, this has shown some potential for the intended ancillary
136 benefits, as one report of CGM with remote monitoring in four patients with COVID-19 in Israel
137 showed a 50% decrease in the number of required bedside glucose measurements, as well as a
138 decrease in the risk of staff exposure and care burden.[30] The feasibility of remote real-time CGM
139 use during COVID-19 was also recently reported by Reutrakul and colleagues.[31] In addition, a
140 reduction in hypoglycemia has also been demonstrated using inpatient remote real-time CGM in
141 a recent trial at the Baltimore VA Medical Center.[32] In this study, patients with T2DM on basal-
142 bolus insulin who were considered at-risk for hypoglycemia were randomized to Dexcom G6
143 CGM with data continuously available to nursing staff in a similar telemetry-like set-up vs.
144 standard inpatient capillary BG checks (approximately four times daily) with a blinded CGM.
145 Among those in the actively monitored CGM group, total per-patient glycemic events <70mg/dL
146 and <54 mg/dL were reduced by 60% (p=0.024) and 89% (p=0.003) respectively compared to
147 standard of care. Reductions were also seen in percent of time spent below <70 mg/dL (0.40%
148 vs. 1.88%, p=0.002) and below <54 mg/dL (0.05% vs. 0.82%, p=0.017). Furthermore, another
149 recent RCT using real-time CGM (G6) showed a modest reduction of time spent in
150 hyperglycemia >250 mg/dL (-11.41%) with a similar approach but including alarms, the TIR
151 (70-180 mg/dl) was 25% for the intervention group and 19.9% in the control group.[33] With a
152 standard protocol using basal-bolus, the TIR (70-180) was ~55% with two different basal
153 insulins.[27]

154 ## 1.2.2 Hybrid closed-loop insulin therapy

155 Hybrid closed-loop (HCL) or automated insulin delivery (AID) systems are one of the newest
156 available technologies for diabetes management, designed to make algorithm-based adjustments
157 to insulin infusion using CGM sensor glucose values and trends to maximize time in target
158 glucose range [time in range (TIR), 70-180 mg/dL]. An insulin delivery device (pump) interacts
159 directly with the CGM to adjust insulin continuously according to need in real-time. The use of
160 HCL therapy is being rapidly incorporated into ambulatory DM management and has been
161 shown to be safe and effective in diverse populations and settings.[34-37] The proposed
162 Omnipod5/Horizon AID system, employing a personalized MPC algorithm, is a novel device
163 that has been evaluated for safety in children and adults with T1DM, performing well under
164 supervised free-living conditions.[35] It has also been shown to cope effectively with common
165 glycemic control challenges in the outpatient setting, including daily physical activity and
166 unrestricted meals in adults with T1DM.[35,36] This system has demonstrated remarkable
167 achievement of glycemic targets in children, adolescents, and adults with T1DM,[35] including in
168 those at the highest risk of hypoglycemia.[36] For example, use of the Omnipod Horizon HCL
169 system resulted in a very low risk of hypoglycemia with a median of 0.9% ± 1.3% of glucose
170 readings <70 mg/dL and 0.09% ± 0.25% <54 mg/dL in adults with T1DM treated as

171   outpatients.[38] They achieved 72.5% TIR (70-180 mg/dL), a mean glucose of 154 ± 15 mg/dL and
172   a coefficient of variation (CV) of 30 ± 6%.[38]

173   The system provides a low rate of hypoglycemia with <2% of sensor glucose readings <70
174   mg/dL, while achieving over 70% TIR.[38] The pediatric subjects in the Omnipod 5 pivotal study
175   entered the study with a mean glucose of 185 ± 23 mg/dL with 51 ± 13.3% TIR.[38] Other initial
176   trials of this AID system showed percentage of TIR above 70% in different age groups with
177   various challenges applied to the AID system **(Table 1)**.

Table 1. Initial studies of the Omnipod5/Horizon AID system.

	G160169	G160169	G170012	G170012	G170143	Omnipod 5	Omnipod 5
IDE	S003	S003	S001	S001	S002	Pivotal – first 4-9 weeks	Pivotal – first 4-9 weeks
Age group (years)	Adults	Adolescents	Adults	Adults	Adults	Adults (14-70)	Pediatrics (6-14)
Challenge	100% meal bolus	100% meal bolus	Meals	Exercise	Free-living	Free-living	Free-living
Sample size (n)	10	12	12	12	11	18	18
Study duration	36 hours	36 hours	54 hours	54 hours	96 hours	4-9 weeks	4-9 weeks
Mean age (yrs)	41.7±18.1	14.6±1.5	35.4±14.2	36.6±14.4	28.3±7.5	35±11	10.6±1.8
DM duration (yrs)	23.7±15.3	4.6±3.3	16.5±9.3	21.6±15.7	13.4±6.0	17±12	5±3
A1C (%)	7.4±0.8	8.2±0.9	7.7±0.9	7.6±1.1	7.4±1.1	7.1±0.8	7.8±0.9
Mean glucose	155.0±14.8	153.4±21.6	153.4±15.3	136.0±14.3	149.7±11.3	155 ± 15	158 ± 10
Sensor Glucose (% time)							
70-180 mg/dL	73.0±15.0	72.6±15.5	76.1±8.0	85.1±9.3	73.7±7.5	73.8 ± 9.1	70.1 ± 5.2
< 50 mg/dL	0.0 ± 0.1	0.2 ± 0.3	0.0 ± 0.1	0.1 ± 0.2	0.1±0.2	0.1 (0.0, 0.2)	0.2 (0.0, 0.5)
< 70 mg/dL	0.7±1.2	2.0±2.4	0.6±0.9	1.4±1.3	1.9±1.3	0.9 (0.5, 1.3)	1.2 (0.9, 2.2)
> 180 mg/dL	26.3±14.4	25.4±16.1	23.3±8.5	13.5±9.5	24.5±7.7	25.0 ± 9.1	28.3 ± 5.2
≥ 250 mg/dL	3.6±3.7	4.9±6.3	4.5±3.6	1.8±2.4	4.5±4.2	5.6 ± 6.1	8.6 ± 4.1

178

179   While some recent efforts have been made to move these new technologies to the inpatient
180   setting to improve hospital diabetes management,[23,24] inpatient data for HCL/AID use is limited.
181   Several studies from the United Kingdom have shown promising results in glycemic control
182   parameters in specific hospitalized populations.[6-8] For example, an inpatient trial by Bally et al.
183   enrolling non-ICU patients with DM showed those assigned to closed-loop therapy achieved
184   65% TIR compared to 41% with usual care (P<0.001) without an associated increase in
185   hypoglycemia.[6] Two recent studies reporting data on glycemic control using real-time CGM in
186   the inpatient setting showed lower percent TIR achieved in this setting for patients on
187   subcutaneous insulin regimens [median TIR 25.31% (11.78-42.97)[33]; mean TIR 56.6 ± 25.6%
188   and 57.5 ± 25.1%[27]].

189   The Omnipod5/Horizon AID system has not been tested in hospitalized adults; however, among
190   available options, we believe it is uniquely fashioned toward assimilation and optimal
191   performance in the inpatient setting. The system provides significant hypoglycemia protection,
192   with an automated "hypoglycemia protect" feature which simultaneously raises the algorithm's
193   glucose target to 150 mg/dL, decreases basal insulin delivery by 50%, and decreases the

194   aggressiveness of any insulin delivery in response to increasing glucose levels. Glucose rate of
195   change information is also accounted for at the time of boluses, such that a reverse correction is
196   calculated and instituted to prevent hypoglycemia when glucose levels are below the target at the
197   time of a bolus insulin dose. As described previously, in the outpatient setting, these have
198   resulted in extremely low rates of hypoglycemia,[38] and will be both practical and valuable in
199   managing patients with variable insulin requirements. Automated features are supplemented by
200   patient-specific physician input, as providers also have control over the insulin-to-carbohydrate
201   ratios (ICR) and correction/sensitivity factors (ISF) for manual dose calculations.

202   Another key aspect of this system that makes it particularly attractive for inpatient use lies in its
203   remote operation capability. Most HCL/AID insulin delivery systems require a physical
204   connection between patient and device wherein the insulin pump is attached to the infusion site
205   cannula by variable lengths of plastic tubing. However, the Omnipod is the only commercially
206   available insulin pump that does not employ any tubing to connect the subcutaneous insulin
207   infusion site to the insulin reservoir; both are contained within the disposable "Pod" worn by the
208   patient. Additionally, the Omnipod5/Horizon AID system employs a physically independent
209   controller (PDM smartphone) that is used to monitor CGM values and HCL functional status,
210   perform infusion site (pod) changes, and manually control insulin infusion when required
211   ("open-loop" setting), while also allowing closed-loop/automated insulin delivery to continue in
212   the physical absence of the controller.[35] This will enable HCW to interact with the pump,
213   including delivering insulin and changing delivery settings from *outside* the patient's room. **As
214   such, this device independence offers a unique opportunity for insulin delivery in the
215   hospital to improve glycemic control with remote management capabilities.**

216   A third key aspect of the Omnipod5/Horizon AID system is that all of the components are
217   intended for single-person use and have relatively low start-up costs compared to other available
218   insulin pumps. The Omnipod5/Horizon AID system (PDM, pod) costs much less than other
219   available closed-loop systems. Pumps used by these other systems can cost on the order of
220    $4,000 to $8,000 and are intended to be used for at least four years before replacement. This
221   makes it possible to use the Omnipod5/Horizon AID system in the hospital without needing to
222   own any component of the system prior to admission, including the insulin pump (PDM). This is
223   especially relevant for patients requiring isolation.

224   Our overarching ***central hypothesis*** is that with the Omnipod 5/Horizon AID system, AID
225   therapy is feasible and safe in the hospital, achieves superior glycemic control compared to the
226   current standard of care, and reduces the frequency of patient-staff encounters associated with
227   PPE use. This protocol is an initial implementation trial to assess feasibility of and barriers to
228   larger-scale inpatient deployment of this system (***Aim 1***) and to describe early experience with its
229   use and glycemic control in the hospital (***Aim 2***). Results generated from this trial will serve as
230   preliminary data in the creation of a large multi-institution randomized controlled trial (RCT) to
231   assess superiority compared to standard of care insulin therapy, including the potential for future
232   use in those with COVID-19 infection or other conditions requiring isolation precautions.
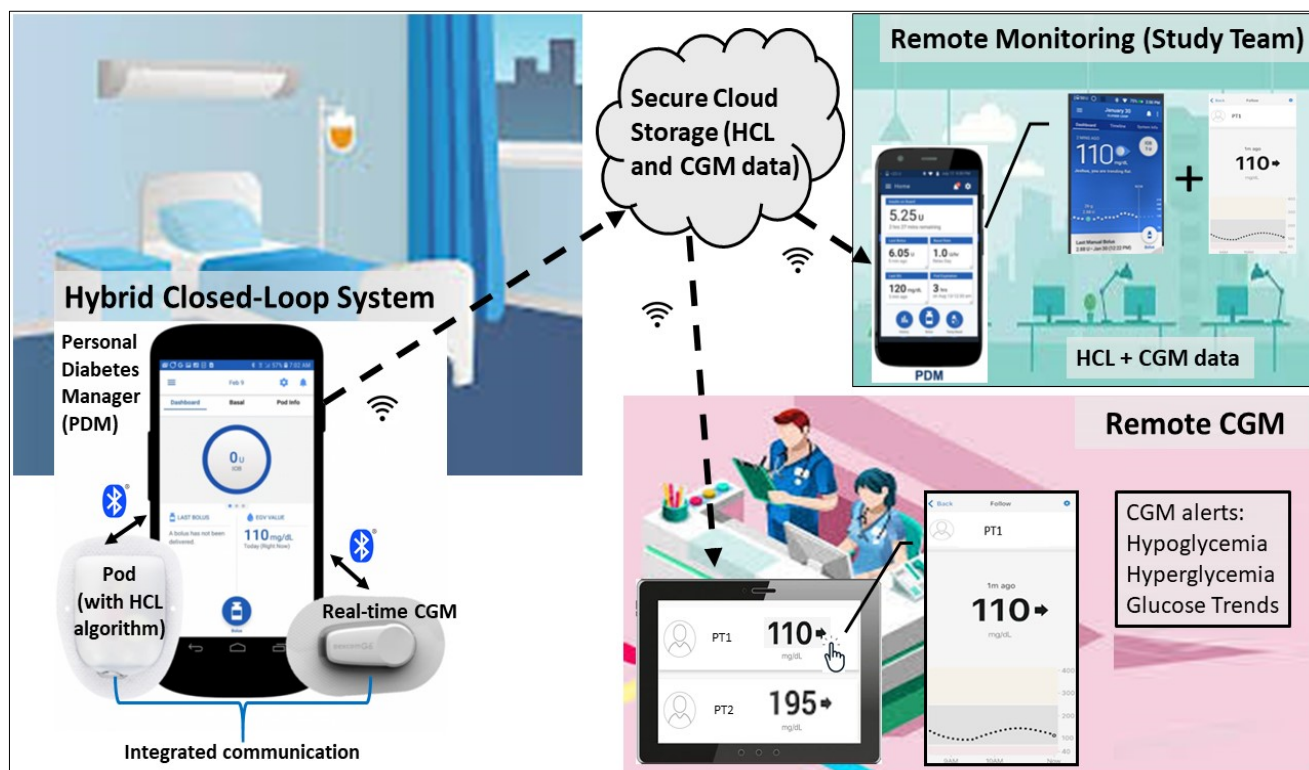
Figure 3. Schematic for Omnipod5/Horizon AID and Dexcom G6 CGM remote monitoring in the hospital.

233   __Aim 1__**: To test the functional operability and applied use of the Omnipod 5/Horizon AID**
234   **system in patients with DM admitted to the hospital (Figure 3).** We will test deployment of
235   the HCL system in each of the three institutions that plan to participate in the eventual RCT.
236   Eighteen patients with pre-existing insulin-treated DM admitted to a non-ICU medical-surgical
237   floor will receive HCL insulin therapy. Glucose monitoring will transition from intensified POC
238   testing (phase 1, n=9) to standard of care POC testing (phase 2, n=9). To investigate operability
239   (**Aim 1.1**), we will specifically examine the proportion of time spent in HCL settings after initial
240   CGM validation, percentage of time with CGM readings, and percentage of bolus or corrective
241   insulin doses given based on CGM values. We will also assess proportion of CGM values within
242   ±15 and 20% of POC reference values for glucose levels >70 mg/dL and ±15 or 20 mg/dL for
243   POC glucose levels ≤100 mg/dL (%15/15, %20/20). To assess perception and identify additional
244   unforeseen barriers to implementation (**Aim 1.2**), patients and hospital staff will be asked to

245 provide intermittent open-ended feedback and structured surveys regarding the use of the AID
246 system.

247 _Hypothesis 1: Inpatient HCL therapy with the Omnipod 5/Horizon AID system functions_
248 _well/consistently in the hospital and is supported by patients and staff._

249 **Aim 2: To assess glycemic control with the Omnipod 5/Horizon AID system in the inpatient**
250 **setting.** To describe glucometric data associated with inpatient HCL use (**Aim 2.1**), we will
251 analyze and report CGM data including percent time in target glucose range (TIR, 70-180
252 mg/dL), number of hypoglycemic (<70 mg/dL) and clinically-important hypoglycemic (<54
253 mg/dL) episodes per patient and per patient-day, percent time below range (TBR, <70mg/dL),
254 percent time in clinically-important hypoglycemia range (<54 mg/dL), percent time above range
255 (TAR, >180 mg/dL), percent time in severe hyperglycemia (>250 mg/dL), coefficient of
256 variation (CV) and standard deviation (SD). To assess HCL initiation settings and the need for
257 setting adjustments in hospitalized patients (**Aim 2.2**), we will evaluate the frequency of
258 adjustments to insulin infusion doses including basal rate, insulin-to-carbohydrate ratio (ICR),
259 and insulin sensitivity factor (ISF) in response to: 1) clinically-important hypoglycemia (<54
260 mg/dL) and 2) prolonged hyperglycemia (>250 mg/dL for >1 hour).

261 _Hypothesis 2: The Omnipod 5/Horizon AID system is safe and provides adequate (>55% TIR)_
262 _glycemic control in non-ICU hospitalized patients._

263 This proposal addresses multiple unique opportunities for the transformation of inpatient
264 diabetes care, including: the **(1)** translation of HCL/automated insulin delivery to the inpatient
265 setting, **(2)** the efficacy of these technologies in improving inpatient glycemic control and rates
266 of iatrogenic hypoglycemia in patients admitted with DM and diverse admission diagnoses, and
267 **(3)** the potential for future studies testing the use of remote HCL and CGM technology for
268 administration of insulin, as it pertains to patients who have isolation precautions, including for
269 COVID-19.

270 **1.3 Preliminary Data**

271 Our preliminary data from a pooled analysis of inpatient CGM studies including 4,067 matched
272 CGM and POC glucose values from non-ICU patients with T1 and T2DM showed an overall
273 mean absolute relative difference (MARD) of 12.8%. The MARD decreased with time as
274 expected (12 hours: 16.4%, 24 hours: 14.4%, All values: 12.8%). The proportion of CGM values
275 with in ±15, 20 and 30% of POC reference values for glucose levels >100 mg/dL and ±15, 20 or
276 30 mg/dL for POC glucose levels ≤100 mg/dL (%15/15, %20/20, %30/30) increased between the
277 first 12-hours (57.0, 69.2, 85.9%) and 24-hours (63, 75.6, 89.2%) of sensor life. The overall
278 proportion of CGM
279 values meeting %15/15,
280 %20/20, %30/30
281 criteria were 68.7, 81.7,
282 93.8%, respectively
283 **(Table 2)**. MARD and
284 median ARD varied
285 according to categories

	CGM vs Capillary POC (first 12 hours)	CGM vs Capillary POC (first 24 hours)	CGM vs Capillary POC (all data)
Paired readings, n	263	627	4067
MARD, %	16.4	14.4	12.8
Median ARD, % (IQR)	12.5	11.1	10.1
%15/15, %20/20, %30/30	57.0, 69.2, 85.9	63.0, 75.6, 89.2	68.7, 81.7, 93.8

Table 2. CGM accuracy metrics in non-critically ill hospitalized patients with diabetes (preliminary data, unpublished

286 of hemoglobin level and POC glucose level strata with minor variations according to renal
287 function categories. The highest MARD was observed for patients with glucose levels in the
288 hypoglycemic range (50-70mg/dL; MARD 14.5%) and for those with severe anemia
289 (hemoglobin <7g/dL; MARD 17.8%), **Figure 4**.
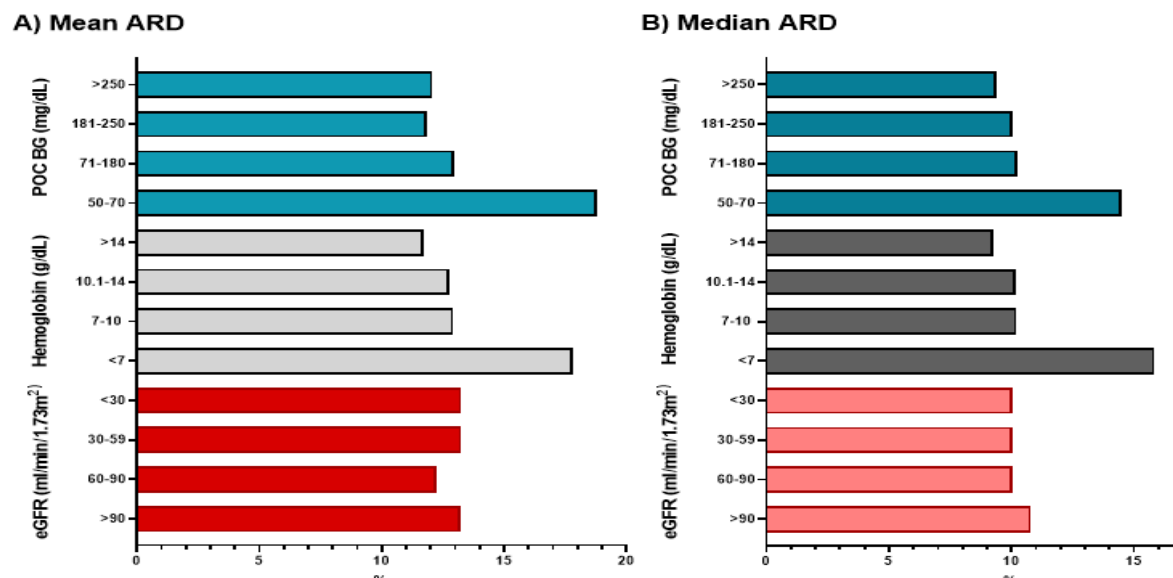
Figure 4. MARD and median ARD comparing CGM with POC in non-ICU hospitalized patients with diabetes, according to eGFR, glucose, and hemoglobin categories (preliminary data, unpublished).

290 A Clarke error grid (CEG) analysis of all matched pair data showed 98.7% of values falling in
291 CEG Zones A+B (Zone A, 80.9%; Zone B, 17.8%; Zone C, 0.1%; Zone D, 1.1%, Zone E, 0.0%),
292 **Figure 5.**

293 At Emory, for patients in the ICU with
294 COVID-19, we have already begun using
295 the Dexcom G6 CGM in conjunction
296 with Glucommander-directed IV insulin
297 therapy. Conceptually, this system
298 parallels closely what we here propose to
299 undertake with HCL therapy. Like HCL,
300 Glucommander uses an algorithm to
301 adjust insulin delivery based upon
302 frequent glucose data input (every 1-2
303 hours); however, in this case, insulin is
304 provided intravenously, as is appropriate
305 for critically ill patients. As such, beyond
306 the CGM, the components of this system
307 differ considerably from the Omnipod
308 5/Horizon, which automates
309 subcutaneous insulin delivery. In our
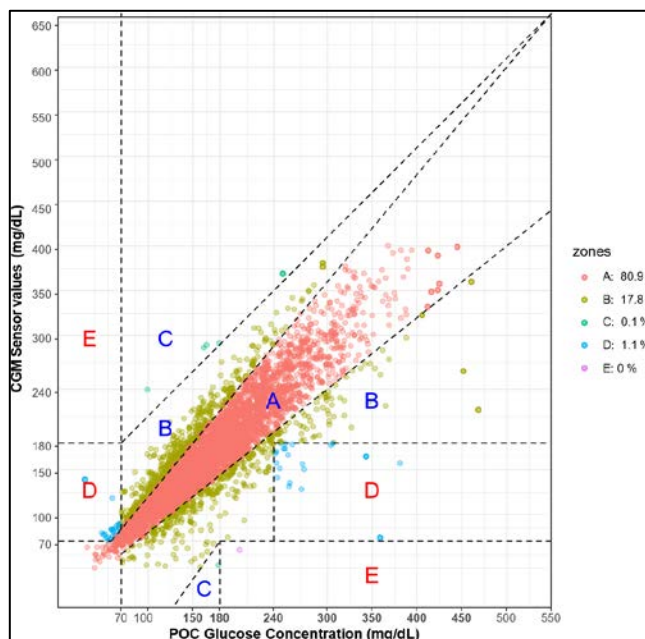
Figure 5. Clark Error Grid analysis of inpatient CGM values compared to POC glucose testing (preliminary data, unpublished).

310

318
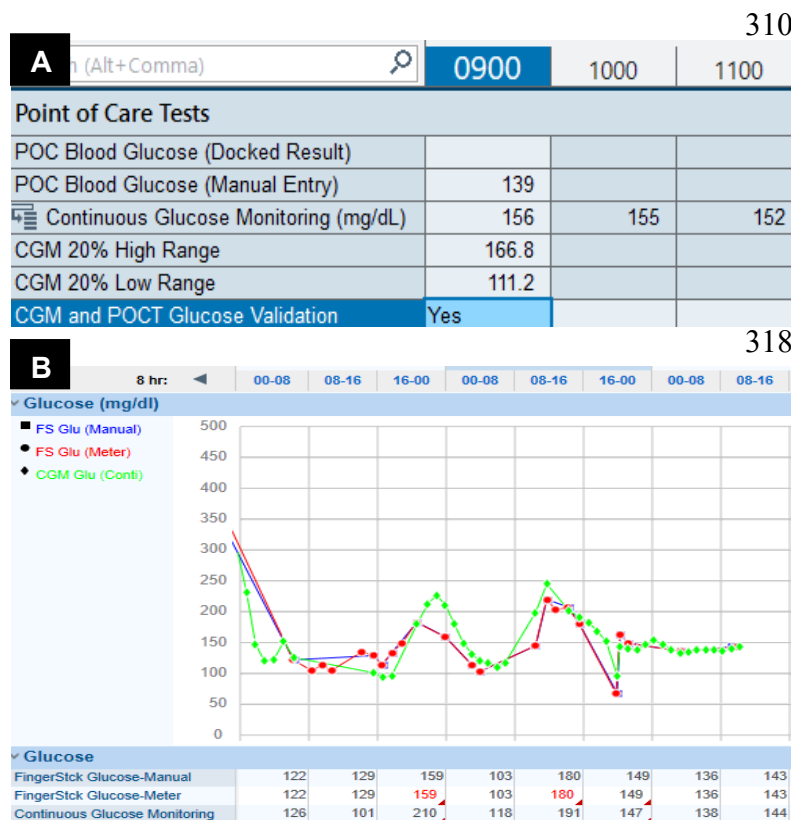
Figure 6. EHR documentation and validation. A) flowsheet shows upper and
lower 20% range of POC to document validation (yes/no), B) remote EHR
access to documented CGM values trend (green) and POC values.

333

early experience with the Dexcom G6/Glucommander system, we have observed reliable adjustments to IV insulin infusion based on the CGM values using an intermittent validation protocol comparing CGM to POC glucose values to ensure ongoing CGM accuracy. We have used a similar protocol for routine validation of CGM readings in the ICU as we have proposed in this study. This involved creation of an embedded glucose documentation and validation tool in the electronic health record (EHR) system (EPIC) itself, which after receiving the necessary POC glucose values, advises nursing staff on the necessary accuracy range in which the CGM glucose value

334 must lie in comparison to the POC glucose entered (±20% for glucose values over 100 mg/dL),
335 **Figure 6.** Criteria were also developed to ensure ongoing sensor reliability, with
336 recommendations to revert back to POC glucose testing in cases of: 1) CGM sensor signal loss,
337 2) loss of CGM trend arrow, and 3) rapid changes in sensor glucose values (>3 mg/dL/min). To
338 investigate feasibility and reliability of the Omnipod5/Horizon AID system in the inpatient
339 setting, we assessed the ability of the pump (pod) and CGM devices to communicate with one
340 another and with the Personal Diabetes Manager (PDM). The PDM is a dedicated android
341 smartphone for the Omnipod5/Horizon and Dexcom applications, which allows for remote
342 control of the insulin pump and reception of CGM glucose values. Reliability of remote bolus
343 insulin delivery and glucose monitoring in COVID-19-specific rooms was tested at Stanford and
344 Emory. The CGM was connected to a "walk-about" sensor simulator and paired with the HCL
345 pod. The CGM and pump (HCL pod) were separated from each other by 3-4 feet to simulate
346 placement on a patient. Because of current PPE shortages, and to avoid unnecessary personnel
347 exposure risk on an active COVID-19 unit, only unoccupied rooms were tested. Communication
348 was tested from the patient inside the room to the PDM stationed outside the room after closing
349 room doors: (1) in different locations within the patient room (including bathroom); (2) with staff
350 personnel acting as an intervening body; (3) in proximity to multiple activated patient care
351 devices with interference potential (telemetry monitor, lights, TV, EKG, ultrasound, iPad, IV
352 pumps); and (4) with variable external PDM locations (wall, hall table). Throughout the testing,

353 and in every room for each configuration, CGM data remained continuous, with stable readings
354 every five minutes. Each remote bolus was transmitted successfully. An 18-hour overnight test
355 was also completed without any lapse in CGM data or HCL functionality at Stanford.

356 **1.4 Potential Risks and Benefits of the [Investigational Device]**

357   **1.4.1 Known Potential Risks**

358 The protocol constitutes greater than minimal risk.

359   **1.4.1.1 Hyperglycemia and Hypoglycemia Risks**

360 The Hybrid Closed Loop System (Omnipod5/Horizon) will have a glucose target lower than
361 what is in the typical range for target glucose in most hospitals. As such, there may be greater
362 risk for hypoglycemia. However, with use of CGM and close monitoring by the study team and
363 hospital staff, this risk should be small. In outpatient studies of patients with T1DM using the
364 Omnipod5/Horizon AID system, the median percent of glucose values <70 mg/dL was
365 <2%. Hypoglycemia, if it occurs, could potentiate a cardiac arrhythmia. If hypoglycemia is
366 severe enough a seizure, loss of consciousness, and even death is possible. These are risks
367 common to all people on insulin therapy.

368 Hyperglycemia is a known risk with having diabetes, and can occur with rapid changes in diet, or
369 the use of medications such as glucocorticoids, or significant worsening of an underlying
370 medical condition which can result in resistance to the effect of insulin on lowering glucose
371 levels. The pod only uses rapid-acting insulins, so if an insulin infusion catheter was dislodged
372 or became kinked or the insulin flow was blocked, then there is an increased risk of developing
373 hyperglycemia and with hours of interrupted insulin delivery this can lead to ketosis or diabetic
374 ketoacidosis (DKA) which can lead to shock, coma, or death. The glucose values will be
375 monitored continuously and remotely by study staff, so prolonged hyperglycemia is unlikely to
376 occur.

377 Hypoglycemia and hyperglycemia could also result if there is over or under delivery of insulin
378 due to a device defect, failure or malfunction of any of the components of the system including
379 communication issues, or sensor issues.

380 Although there is potential for harm from glucose management that is more intensive with a
381 lower glucose goal than standard glucose management, the potential benefit exceeds the potential
382 risk since outcomes of hospitalized diabetic individuals with uncontrolled dysglycemia
383 frequently are poor.

384 Once the study is completed, participants will need to be transitioned from AID to a
385 subcutaneous insulin regimen. The study team will have knowledge of insulin doses delivered by
386 the Omnipod 5/Horizon AID system, which will be converted into a standard basal-bolus insulin
387 regimen with corrective insulin. This transition to usual care could result in episodes of
388 hypoglycemia or hyperglycemia.

389 We do not foresee any long-term risks from participating in this study.

390 The study principal investigators at each site will be closely monitoring for hypoglycemia,
391 hyperglycemia, and device function (errors or failures). The site investigator will be notified
392 when the amount of hypoglycemia exceeding a pre-specified threshold has occurred. Any severe
393 hypoglycemia, DKA, or unanticipated device issues will be reviewed by the Medical Monitor.

394 **1.4.1.2 Other risks**

395 Insertion of the pod infusion set catheter and/or the sensor wire can result in bruising,
396 bleeding, redness, induration, infection, pain and discomfort. The adhesives used to secure the
397 pod and CGM sensor can cause local skin reactions, itching, redness, and allergic reactions to the
398 adhesives.

399 On rare occasions the CGM sensor wire may break off or be retained under the skin. Rarely this
400 could cause local redness, swelling, or pain at the insertion, and even require surgical removal.

401 Blood draws as well as fingersticks for blood glucose monitoring are part of routine care, but are
402 also required by this study. Blood draws and fingersticks may cause local pain, bruising and
403 rarely can result in an infection or fainting.

404 Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Data
405 downloaded from the CGM and AID device will be collected for the study as measures of
406 diabetes self-management behaviors. Some people may be uncomfortable with the researchers'
407 having such detailed information about their daily diabetes habits or with the questionnaires.

408 **1.4.2 Known Potential Benefits**

409 There are recognized benefits to simply being in a clinical study, including close clinical
410 monitoring. The use of AID offers the prospect of direct benefit. As described above in this
411 protocol, AID therapy is a Food and Drug Administration (FDA) approved therapy for T1DM in
412 people 7-75 years of age with other AID systems. However, its efficacy in treating hospitalized
413 patients with DM or inpatient hyperglycemia is unknown. At this time, it is not the standard of
414 care for hospitalized patients.

415 AID may benefit patients if improved glucose control is achieved that reduces the incidence of
416 adverse outcomes due to infection or other conditions that lead to the need for
417 hospitalization. The information generated by the study will have generalizable value to adults
418 with insulin needs who are hospitalized for serious illnesses. If this therapy is well accepted by
419 hospital personnel and hospital physicians, it could become the standard of care for patients with
420 DM who are hospitalized and require insulin therapy. The risk to patients is relatively small and
421 the potential benefit is great if improved glucose control reduces the incidence of adverse
422 hospital outcomes.

423 **1.4.3 Risk Assessment**

424 The risks for events such as DKA and severe hypoglycemia are no greater, and possibly less
425 likely, with use of AID therapy compared with usual care not using a HCL system. The study
426 offers the prospect of direct benefit, including the potential for improved glycemic control. Study
427 team and nursing staff will also be using CGM remote monitoring of their glucose values, which

428   should reduce the risks of severe low blood glucose levels or prolonged high glucose levels. In
429   addition to monitoring, the CGM validation procedures described in section 3.1 mitigate the risk
430   of bolus or corrective insulin dosing based on an inaccurate CGM reading. Therefore, this
431   protocol is consistent with the United States Department of Health and Human Services,
432   Protection of Human Subjects, Subpart D, section 46.405 (research involving greater than
433   minimal risk but presenting the prospect of direct benefit to the individual subjects involved in
434   the research).

435   **1.5 General Considerations**

436   The study is being conducted in compliance with the policies described in the study policies
437   document, with the ethical principles that have their origin in the Declaration of Helsinki, with
438   the protocol described herein, and with the standards of Good Clinical Practice (GCP).

439   When feasible, data will be directly collected in electronic case report forms (CRF), which will
440   be considered the source data.

441   The protocol is considered a significant risk device study, due to the fact that the use of the
442   Omnipod5/Horizon AID system is experimental and not approved for use in a hospital setting.
443   The Dexcom G6 sensor is also not approved for use in a hospital setting. Therefore, an
444   investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is
445   required to conduct the study.

Chapter 2: Study Enrollment and Screening

446

2.1 Participant Recruitment and Enrollment

447

448 Enrollment will proceed with the goal of at least 18 patients completing the study. Up to 30
449 patients may be enrolled to achieve this enrollment goal. Study participants will be recruited
450 from 3 clinical centers in the United States and no clinical centers outside the United States. All
451 eligible participants will be included without regard to gender, race, or ethnicity.

452 Potential study participants will be identified clinically from the hospital service for people
453 admitted with insulin-treated DM (T1 or T2) requiring inpatient insulin therapy, and from
454 consults sent to the endocrine service for hyperglycemia management. After a potential
455 candidate for enrollment in the study is identified, their primary physician/inpatient team will be
456 contacted to see if they would like to have the patient approached about the study. If so, one of
457 the research staff, coordinator or research physician will explain the study to the patient to see if
458 they are interested in participating.

459 <u>Participants</u>: Eligible patients meeting inclusion and exclusion criteria as described below will
460 be invited to participate during hospital admission. IRB-approved informed consent will be
461 obtained by study personnel designated at each site (**Figure 1**).

462 ▪   Three sites will participate in this study (Emory, Stanford, UVA).
463 ▪   Eighteen patients will be included; up to 30 patients may be enrolled to achieve
464 this enrollment target (accounting for possible early hospital discharge, mortality and
465 study withdrawal).
466 ▪   Enrollment will proceed stepwise as below:
467 ▪   <u>Phase 1:</u> Nine patients will receive AID (Omnipod 5/Horizon HCL with Dexcom
468 G6 CGM) combined with intensified POC glucose monitoring (standard of care before
469 meals and at bedtime, adding overnight glucose assessments at approximately 12AM and
470 3AM, or approximately every 4 hours as clinically indicated).
471 ▪   <u>Phase 2:</u> Nine patients will receive AID combined with standard-of-care POC
472 glucose monitoring (before meals and bedtime, or approximately every 6 hours as
473 clinically indicated).

2.2 Informed Consent and Authorization Procedures

474

475 Potential eligibility may be assessed as part of a routine-care examination. Before completing
476 any procedures or collecting any data that are not part of usual care, written informed consent
477 will be obtained.

478 For potential study participants the study protocol will be discussed with study staff. The
479 potential study participant will be given the Informed Consent Form to read. Potential study
480 participants will be encouraged to discuss the study with family members and their personal
481 physicians(s) before deciding whether to participate in the study.

482 As part of the informed consent process, each participant will be asked to sign an authorization
483 for release of personal information. The investigator, or his or her designee, will review the

484 study-specific information that will be collected and to whom that information will be disclosed.
485 After speaking with the participant, questions will be answered about the details regarding
486 authorization.

487 A participant is considered enrolled when the informed consent form has been signed.

2.3 Participant Eligibility

2.3.1 Inclusion Criteria

490 Individuals must meet all of the following inclusion criteria in order to be eligible to participate
491 in the study.

492 ▪ Any patient ≥18 years of age with insulin-requiring T1 or T2DM admitted to
493 general (non-ICU) medical-surgical hospital service requiring inpatient insulin therapy.

2.3.2 Participant Exclusion Criteria

495 Individuals meeting any of the following exclusion criteria at baseline will be excluded from
496 study participation.

497 ▪ Patients admitted to ICU
498 ▪ Patients anticipated to require less than 48 hours admission
499 ▪ Evidence of hyperglycemic crises (diabetic ketoacidosis or hyperosmolar
500 hyperglycemic state)
501 ▪ Severely impaired renal function (eGFR < 30 ml/min/1.73m^2) or clinically
502 significant liver failure
503 ▪ Severe anemia with hemoglobin <7 g/dL
504 ▪ Evidence of hemodynamic instability
505 ▪ Hypoxia (SpO2 <95% on supplemental oxygen)
506 ▪ Pre-admission or inpatient total-daily insulin dose >100 units daily
507 ▪ Mental condition rendering the participant unable to consent or answer
508 questionnaires
509 ▪ Pregnant or breast-feeding at time of enrollment
510 ▪ Unable or unwilling to use rapid-acting insulin analogs (Humalog, Admelog,
511 Novolog or Apidra) during the study
512 ▪ Use of hydroxyurea or high dose ascorbic acid (known interference with CGM
513 system)
514 ▪ COVID -19 infection or Person under investigation (PUI) on isolation precautions

2.4 Screening Procedures

516 After informed consent has been signed, a potential participant will be evaluated for study
517 eligibility through the elicitation of a medical history, performance of a physical examination by
518 study personnel and local laboratory testing (if needed) to screen for exclusionary medical
519 conditions.

520 **2.5 Data Collection and Testing**

521 Admitting vital signs and height and weight measurements will be recorded. A limited physical
522 exam to assess the participant's skin and suitability for wearing the study devices will be
523 performed by the study investigator or designee (a physician, resident/fellow, nurse practitioner
524 or a physician assistant).

525 The following procedures will be performed/data collected/eligibility criteria checked and
526 documented:

527 •   Inclusion and exclusion criteria assessed
528 •   Demographics (date of birth, sex, race and ethnicity)
529 •   Contact information (retained at the site and not entered into study database)
530 •   Medical history
531 •   Substance use history (drinking, smoking, and drug habits)
532 •   Concomitant medications
533 •   Physical examination to include:

534   ◆   Weight, height
535   ◆   Vital signs including measurement of blood pressure and pulse

536 •   Blood glucose obtained at time of admission to the hospital if on insulin prior to
537 admission, or blood glucose at the time insulin therapy was started in the hospital
538 •   Record latest O_2 saturation if one has been obtained
539 •   Order HbA1c if one has not been ordered
540 •   Order Creatinine if one has not been ordered
541 •   Urine or serum pregnancy test for all women who have reached menarche and are
542 premenopausal and are not surgically sterile

543 **2.5.1 Daily data recording**

544 Each day the medications given will be recorded in our database, with the time and dose of
545 the medication. The lowest O_2 saturation, Hct, and highest creatinine will be recorded if they
546 were obtained.

547 The date and time of any laboratory measurements of serum glucose will be recorded into
548 our database

Chapter 3: Study Procedures

550 **3.1 Omnipod 5/Horizon automated insulin delivery system**

551 All participants will receive treatment with the Omnipod Horizon AID system with integrated
552 Dexcom G6 CGM. These devices will communicate with a patient-specific Samsung smartphone
553 (the PDM) secured outside of the patient room and remotely monitored by nursing station and
554 study team (see **Figure 3**). HCL therapy will continue until discharge or for 10 days from
555 enrollment, whichever is shorter (see discontinuation below). Study procedures will be

556 conducted in medical-surgical floors where study team has provided dedicated in-service
557 training.

558 Nursing staff in medical-surgical units (AM and PM shifts) will receive dedicated in-service
559 training about the technology and the study protocol. Once a patient is identified by the study
560 team, the nursing staff on the floor will be notified the patient will be on automated insulin
561 delivery. The nurse who will be working with the patient will receive an additional review of
562 study procedures and the devices being used. Specific training will be focused on responding to
563 sensor alerts, and how to give a meal bolus and/or a correction insulin dose (using CGM vs POC
564 glucose value). The nursing staff will notify the research staff for any device alarms. Study
565 investigators will document enrollment of the patient in the EHR and provide nursing staff with
566 24-hour contact information. The nurse will be instructed on how to respond to a hypoglycemic
567 alarm, by obtaining a point of care meter glucose reading, and treating as per hospital standard of
568 care if the meter BG is <80 mg/dL.

569   Specific topics that will be reviewed with the nurse taking care of the patient:

570   1) How to give a bolus using the bolus calculator on the Horizon app using the
571   CGM glucose or a meter BG reading if the CGM reading does not meet
572   accuracy criteria.
573   2) How the home screen appears when the subject is in open or closed-loop
574   3) How to assess if the CGM is working properly, i.e. showing a glucose reading
575   and trend.

576 Research staff will initiate the system and replace any components of the system requiring
577 replacement during the study (pods or sensors). Research staff will be notifying the nurse when
578 there is hyperglycemia and the need for a correction dose.

579 Patients will not interact with the AID system and will not be provided access to real-time CGM
580 glucose data for self-monitoring. Patients would not receive training or learn how to use the AID
581 system for insulin delivery. The AID and CGM devices for control and monitoring will be
582 secured in a locked container outside of the patient room to prevent unauthorized access to the
583 system. Only trained personnel will be provided access. The secured PDM will be placed within
584 approximately 15 feet of the patient to minimize potential for signal loss. Should the PDM not be
585 communicating with the Pod/CGM, the research and nursing teams will receive an alert for
586 signal loss >30 minutes to ensure communication is re-established.

587 NOTE: communication with the PDM is not necessary to maintain closed-loop functionality, but
588 is necessary for delivering bolus insulin and for remote system monitoring.

589 Horizon app setup and AID initiation (to be performed by research staff):

590   • For safety, a unique identifier will be assigned to the patient and entered into the Horizon
591   App.
592   • Basic set up will be verified including correct date and time. Two-person verification of
593   pump settings for ICR, ISF, and basal rates will be individually customized and thereafter

594 adjusted for each patient by the study investigators using their clinical judgment. The target
595 glucose will be set to 120 mg/dL initially. **The appropriateness of these settings will be**
596 **reviewed every 24 hours by the research physicians at each site.**
597 • Initial basal rates will be determined using either 60% of current total daily insulin
598 dose (TDD) or 50% of weight-based TDD estimate if not on insulin prior to admission.
599 • Pod application instructions: Fill a pod, clean skin, place pod, then activate pod. Do
600 not enter sensor transmitter ID until the sensor has been activated on the Dexcom app.
601 • The pump can remain in manual mode. A temporary basal rate may be required if the
602 patient has long acting insulin on-board.
603 • To determine where the Dexcom sensor will be inserted and where the pod will be
604 inserted. They should be "in line of sight" of each other, and in areas where the patient is
605 unlikely to be laying on them.
606 • Dexcom G6 sensor will be inserted as per the user manual. The transmitter ID will be
607 recorded and entered into the Dexcom app on the PDM. The sensor will be inserted and
608 activated using the sensor code. The sensor code will be recorded in the sensor log. Share
609 function will be activated and the nursing station remote monitoring tablet will be invited to
610 follow, as well as the approved research team members. Sensor alerts will be set for a
611 threshold of <80 mg/dL, and >250 mg/dL.
612 • Once the sensor has been activated on the Dexcom app, the transmitter ID can be
613 activated on the Horizon app. Automated insulin delivery will not commence until the
614 Dexcom CGM accuracy is validated (see below).
615 • The PDM will be kept in a locked container outside of the patient's room, within
616 approximately 15 feet of the patient.

617 **3.1.1 Dexcom CGM validation**

618 • All blood glucose values used to validate the CGM sensor glucose values will
619 result from hospital point-of-care glucometers. The type of glucometer used by the
620 hospital will be documented in the study source documentation.
621 • CGM validation should *not* be attempted during times of rapid glucose
622 fluctuations (indicated by one or more vertical CGM trend arrows). In this event,
623 assessment will be attempted after stabilization of glucose, indicated by a single
624 horizontal or angled CGM trend arrow.
625 • **Validation will be performed at the initiation of a new sensor/transmitter**
626 **session and confirmed if the CGM sensor glucose value satisfies the below criteria:**
627 o CGM glucose is within the range of 20% of BG for BG values **≥70 mg/dL**
628 *[Validation range: (BG x 0.8) to (BG x 1.2)]*
629 o CGM glucose is within the range of 20 mg/dL of BG for BG values **<70**
630 **mg/dL** *[Validation range: (BG – 20) to (BG + 20)]*
631 • Once validation is confirmed, the patient will be transitioned to HCL/AID mode.
632 • If validation criteria are not met within the first 12 hours of sensor wear, the CGM
633 will be calibrated with the POC glucose value, and the system will remain in the
634 manual/open-loop setting. Reassessment for CGM validation will occur every 2 to 8
635 hours until criteria are met, or until an additional 12 to 24 hours has elapsed. If 12 to 24
636 hours pass following calibration without a successful validation, a new sensor will be
637 placed, and the process will be reattempted.

638 • If a successful CGM validation is not achieved after 48 hours despite the above
639 measures, the patient will instead be placed on standard insulin therapy under the care of
640 the primary admitting service.

641 **3.1.2 Ongoing glucose monitoring**

642 POC glucose monitoring will be determined based on stepwise enrollment phase as below:

643 Phase 1: POC glucose monitoring will occur at a minimum of 6x per day (below) as clinically
644 appropriate

645 - Before meals, at bedtime, approximately 12AM and 3AM or
646 - Approximately every 4 hours

647 Phase 2: Standard of care POC glucose monitoring with additional POC tests as clinically
648 appropriate

649 - Before meals and at bedtime or
650 - Approximately every 6 hours

651 **CGM values will be validated as above and prior to any meal or correction insulin bolus.**
652 The CGM glucose value will be compared to a concurrent POC glucose value to verify device
653 accuracy (validation criteria as above). If validation criteria are not met by the CGM glucose
654 value, the POC glucose value will be used for bolus or correction insulin dose calculation by the
655 HCL/AID system in lieu of the CGM glucose value.

656 **At investigator discretion, or if >3 consecutive CGM values do not meet validation criteria**
657 **during ongoing POC glucose monitoring after initial validation, calibration or sensor**
658 **change will be performed.**

659 Insulin boluses will be given remotely by nursing staff or study team, but doses will be
660 calculated by the HCL/AID system based on current CGM or POC glucose information and
661 carbohydrate content of meal or snack. Correction boluses will also be delivered as advised by
662 the HCL/AID system.

663 POC glucose assessments will be used instead of CGM sensor values in the setting of: 1) CGM
664 signal loss for >1 hour, 2) loss of CGM trend arrow for >1 hour, and 3) any concerning clinical
665 status changes. The pump will be transitioned to manual/open-loop mode until the issue is
666 corrected or the patient's clinical status is deemed appropriate by study investigators for
667 transition back to HCL/AID mode.

668 **3.1.3 Insulin Delivery**

669 *Nursing Training:* Nursing staff and hospital staff working with these patients will receive
670 training on how the AID system works, and how to administer insulin boluses, and how to
671 change an OmniPod5 pod (see competency checklist for health care professionals for using
672 the AID system in appendix A).

673 • _Basal_: Basal insulin delivery settings will be initiated and adjusted at the discretion of
674 the study investigators. Basal infusion rates will be dictated by the HCL algorithm when in
675 automated (closed-loop) mode.
676 • _Prandial_: Nursing staff will bolus prandial insulin calculated by the HCL/AID system
677 from current validated CGM (or POC) glucose value and meal size/carbohydrate content
678 using the pre-set ICR.
679 • _Corrective:_ Non-mealtime correctional boluses will be calculated by the HCL system
680 (or determined by the pre-set ISF in open-loop settings), and will be given under the
681 guidance of the research team.
682 o NOTE: No CGM-based insulin dosing calculations will be made or administered if
683 CGM validation is not completed and active.
684 • _Target Glucose:_ The target glucose will initially be set at 120 mg/dL. It is adjustable
685 to targets between 110 to 150 mg/dL, and it can be programmed to have higher or lower
686 targets at different times of the day. The research staff will use their clinical judgement to
687 modify the glucose targets for patient safety or to improve glycemic control.
688 • HCL/Automated Mode: in this mode, validated CGM values are used by the device
689 algorithm to automatically adjust insulin infusion rates to target glucose value of 120 mg/dL.
690 • Open-loop/Manual Mode: in this mode, insulin delivery depends only on preset basal
691 rates, ICR, ISF and DIA; no CGM glucose data is required, but may be utilized for insulin
692 dose decisions.

693 **3.2 Unit-based monitoring**

694 CGM data will be available to nursing staff at the nursing station on a dedicated tablet screen (or
695 smartphone) and can also be viewed on the PDM stationed outside the patient room in a locked
696 container.

697 • Nursing staff working with these patients will receiving training on using CGM
698 data and will complete a competency checklist (Appendix A).
699 • CGM alerts will be programmed at the nursing station (tablet) and on the PDM to
700 alarm for glucose values <80 mg/dL. PDMs will be mobile, as they will need to move
701 with the patient for any transfers.
702 • For hypoglycemia alarms (CGM glucose <80 mg/dL), nursing staff will assess the
703 patient and perform POC BG. If concurrent POC BG is <80 mg/dL, patient will be
704 treated by institutional hypoglycemia protocol. If concurrent POC BG is >100 mg/dL,
705 POC BG will be reassessed in 1 hour. If CGM glucose remains in hypoglycemic range,
706 but repeat POC BG remains discordant (>80 mg/dL), the study team will be contacted for
707 further recommendations.
708 • Battery on PDM will be assessed and charged at least daily.

709 **3.3 Remote monitoring by research staff**

710 • The Dexcom Share app for research staff will be set to alarm for hypoglycemia as
711 above, as well as for CGM glucose values >250 mg/dL for >1 hour. The research staff
712 will review patient glucose values, insulin delivery and patient status and determine if a
713 corrective dose of insulin is indicated.

714   •   For unexplained hyperglycemic range CGM values (>300 mg/dL) exceeding 60
715   minutes, POC glucose values will be obtained hourly for those with T1DM and every 2
716   hours for those with T2DM to minimize the risk of hyperglycemic crises. If the CGM
717   glucose remains above 300 mg/dL [>1 hour in T1DM or > 2 hours in T2D] following a
718   corrective insulin dose by the AID system, the study team will be alerted and additional
719   correction action will be taken, with the nursing staff assessing the infusion site, changing
720   the pod or initiating alternative insulin delivery methods (i.e. subcutaneous injections or
721   IV insulin infusion).
722   •   Ketones will be assessed at the discretion of the study physician or primary
723   hospital service for any concern about possible ketosis or DKA by drawing a serum
724   sample (beta-hydroxybutyrate) to be processed at the hospital laboratory.
725   •   Study team will be alerted if there are no CGM readings for 30 minutes and will
726   contact the floor teams to assess the situation and reestablish communication.

727 **3.4 Interruption of HCL Therapy**

728 **Imaging/Procedures:** if pump and CGM must be removed for any incompatible
729 imaging/procedure (e.g. CT, MRI, surgery, electrocautery), management will depend on length
730 of required discontinuation:[39-41]

731   ▪   *Short: <1 hour*
732   BG 180-300: administer corrective bolus insulin
733   If BG is >300: consider transition to IV insulin infusion or continued subcutaneous
734   correction protocol
735   ▪   *Intermediate: 1-3 hours*
736   BG 110-180: administer bolus insulin equal to 70% of the sum of basal rate over the
737   prior 2-3 hours (do not administer if BG is <110).
738   BG 180-300: administer corrective bolus insulin
739   If BG is >300: consider transition to IV insulin infusion or continued subcutaneous
740   correction protocol
741   ▪   *Long: >3 hours*
742   Consider transition to IV insulin infusion or continued subcutaneous insulin regimen
743   within 1 hour of pump discontinuation and determine ability to transition back to
744   HCL post-procedure.
745   **Surgical intervention:** patients will discontinue HCL insulin therapy and will be
746   treated with subcutaneous or IV insulin as per hospital perioperative glycemic
747   management protocol.

748 **ICU transfers:** patients requiring ICU transfer for any reason will be managed by ICU team
749 for diabetes management (i.e. subcutaneous insulin or continuous intravenous insulin
750 infusion). HCL/AID will be discontinued, but use of the Dexcom CGM for glucose
751 monitoring may be continued at ICU team discretion. Upon transfer out of the ICU, patients
752 may resume HCL therapy for diabetes management when appropriate. Patients with
753 worsening clinical condition (hypoxia or hemodynamically unstable) who do not meet ICU
754 transfer criteria may resume the AID system once those conditions are under control.

755 Emergency use of insulin for non-glucose-related indications: in the event that a patient requires
756 insulin for a non-glucose-related indication, such as an IV insulin dose for the treatment of
757 hyperkalemia, HCL therapy should may be suspended temporarily at the discretion of the
758 investigator until confirmed resolution of the underlying condition (e.g. hyperkalemia resolves).
759 If HCL therapy is suspended for >6 hours, the patient should be transitioned to and maintained
760 on subcutaneous insulin until the underlying condition resolves and HCL therapy can be
761 resumed.

762 **3.5 Discontinuation of HCL/AID**

763 Criteria for discontinuation of HCL therapy for an individual participant, as well as study hold
764 parameters are detailed below in sections *6.6.1* and *6.6.2*.

Chapter 4: Study Devices

765

4.1 Description of the Investigational Device

766

767 The Omnipod5/Horizon™ System is composed of three primary components (**Figure 7**):

768 ▪ Omnipod5/Horizon™ Controller – Horizon App (PDM) and Algorithm
769 ▪ Omnipod5/Horizon™ Alternate Controller Enabled (ACE) Pump – Pod
770 ▪ Dexcom G6 – CGM

771 The Omnipod5/Horizon™ System will provide automated insulin delivery when connected to a
772 Dexcom G6 CGM. The system is expected to reduce hypoglycemia without incurring an
773 unacceptable increase in hyperglycemia and mean glucose. The system is also expected to reduce
774 the extent and magnitude of hyperglycemia associated with meals. Optimal post-prandial control
775 requires the user to deliver meal boluses as in current "open-loop" therapy, but the normal
776 operation of the control algorithm will be expected to compensate for mismatched meal boluses
777 and prevent prolonged hyperglycemia. The system uses a control-to-target strategy that attempts
778 to achieve and maintain a set target glucose level, with target setpoints at 110 mg/dL, 120
779 mg/dL, 130 mg/dL, 140 mg/dL and 150 mg/dL. Target setpoints can be adjusted by the
780 user/healthcare provider, and patterns of higher or lower setpoints at different times of the day
781 can be programmed into the Horizon application.

782
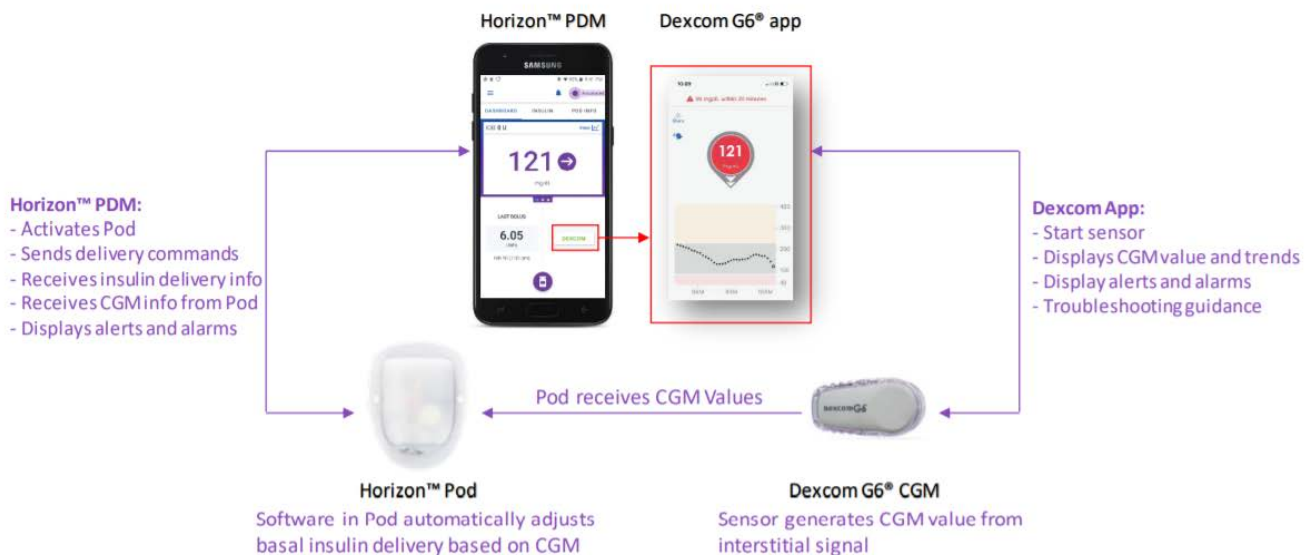
Figure 7. Components of the Omnipod5/Horizon AID and Dexcom G6 CGM system.

783 The Omnipod5/Horizon™ Controller is composed of two parts: the Horizon application ("app")
784 and the model predictive control (MPC) algorithm on the Pod. The MPC algorithm provides
785 insulin micro-boluses once every 5 minutes based upon the predicted glucose over a 60-minute
786 prediction horizon. Optimal post-prandial control will require meal boluses in the same manner
787 as current pump therapy, but normal operation of the MPC algorithm will compensate for late or
788 missed or underestimated meal boluses and mitigate prolonged hyperglycemia. The MPC
789 algorithm uses the control-to-target strategy to achieve and maintain a set target glucose value,
790 thereby reducing the duration of prolonged hyperglycemia and hypoglycemia. The MPC

791 algorithm resides on the Pod (Pump) component of the Omnipod5/Horizon™ System (similar to
792 the DASH alternate controller enabled (ACE) pump cleared in K191679, as described further
793 below).

794 The Horizon™ app will be the primary interface and will be used to start and stop a Pod,
795 program basal and bolus calculator settings for manual mode as well as program settings specific
796 for Automated Mode (hybrid closed-loop).

797 *Manual ("Open-loop") Mode:*

798 In Manual Mode, the Omnipod5/Horizon™ System will function equivalently to the Omnipod®
799 DASH System, which was first cleared under K180045, most recently under K191679. This
800 includes delivering insulin at programmed basal rates and bolus amounts with the option to set
801 temporary basal profiles. The Omnipod5/Horizon™ Controller will also have the ability to
802 function as a sensor augmented pump in Manual Mode, using sensor glucose data provided by
803 the CGM to populate the bolus calculator.

804 *Automated ("Hybrid closed-loop") Mode:*

805 In Automated Mode, the system will support the use of multiple target glucose values, currently
806 intended to be 110-150 mg/dL in 10 mg/dL increments. The research team will program basal
807 rates, glucose targets and bolus calculator settings (see section 3.2). These in turn will inform the
808 MPC algorithm for insulin dosing parameters. The insulin dosing parameters will be adapted
809 over time based on the total daily insulin (TDI) delivered during each Pod use. A temporary
810 hypoglycemia protection mode (Hypo Protect) may be implemented by the user for various time
811 durations during Automated Mode. With Hypo Protect, the algorithm reduces insulin delivery
812 and is intended for use over temporary durations when insulin sensitivity is expected to be
813 higher, such as with discontinuation of steroids, or a significant improvement in illness-related
814 stress, and exercise for ambulatory patients. This function would be enabled at the discretion of
815 the research physicians.

816 The Omnipod5/Horizon™ System will include two apps on a locked-down smartphone (the
817 Samsung J3), referred to as Personal Diabetes Manager (PDM): the Horizon App and the
818 Dexcom App. This phone has shown good communication between the Pod and Dexcom G6
819 sensor in the hospital setting, communicating from the hallway to far corners of the patient's
820 room (including bathrooms), with multiple hospital monitoring devices and pumps functioning in
821 the room. The Horizon App, which will have a similar interface to the cleared Omnipod® DASH
822 System (K191679), will allow the use of large text, graphics, and on-screen instructions to
823 prompt the user through set-up processes. It will also be used to program the user's custom basal
824 insulin delivery profile, check the Pod status, initiate bolus doses of insulin, make changes to a
825 patient's insulin delivery profile, handle system alerts and alarms, and enter Automated Mode.

826 The Dexcom App interface is identical to the current app of the interoperable Dexcom G6
827 Continuous Glucose Monitoring System (K191450) and will provide CGM data, alerts, and
828 alarms to the user.

829   The Horizon App and Dexcom App will not directly communicate with one another. Instead, the
830   CGM transmitter will communicate estimated glucose values (EGV) directly to the Pod. The
831   Dexcom transmitter number must be entered into the Horizon App, and this information is sent
832   to the Pod to allow transmission of EGV. The Pod will pair directly to the transmitter to receive
833   EGV for the algorithm and also sends the EGV back to the Horizon App as shown in **Figure 7**.

834   The Omnipod5/Horizon™ Controller provides the ability to calculate a suggested bolus dose
835   through the use of the bolus calculator. The bolus calculator will have the option to use the EGV,
836   which is communicated to the app via the Pod. If the sensor has passed validation criteria for the
837   day, it is preferred that the EGV be used for correction and meal boluses, since the algorithm will
838   also use the sensor rate of change information in calculating the insulin dose. This allows for
839   less insulin delivery when the estimated glucose is decreasing and more insulin delivery when
840   the estimated glucose is increasing. Insulin-on-board (IOB) is calculated by the algorithm taking
841   into account any manual bolus and insulin delivered by the algorithm.

842   As with the cleared Omnipod® DASH System, Insulet will utilize a proprietary encrypted
843   security stack embedded within the Bluetooth Low Energy (BLE) communication.

844   **4.1.1 Omnipod5/Horizon™ automated insulin delivery system**

845   The Pod component of the Omnipod5/Horizon™ System is similar to the Omnipod® DASH
846   ACE Pump cleared under K191679. Compared to the DASH ACE Pump (K191679), the
847   Horizon™ ACE Pump (Pod) has additional software to optimize communication to accept inputs
848   from the CGM (Dexcom G6) and the Horizon™ Controller. The insulin delivery mechanism and
849   the patient and fluid contacting components are identical to the DASH Pod.

850   The Pod is a lightweight, self-adhesive device that the user fills with U-100 rapid-acting insulin
851   and wears directly on their body. The Pod delivers insulin into the user's body through a small
852   flexible tube, called a cannula, based on the commands from the compatible controller. In the
853   Omnipod5/Horizon™ System, the Pod will house the MPC algorithm and communicate directly
854   with the CGM and the Horizon App. The algorithm commands the Pod's insulin delivery in the
855   form of micro-boluses based on predicted glucose values. As with the cleared Omnipod® DASH
856   System, the Pod of the Omnipod5/Horizon™ System will come pre-packaged in a sterile
857   container with a fill needle and a fill syringe. **Figure 8** below is a representation of the Pod. The
858   Omnipod5 has not been approved for commercial sale and has not been tested for use on
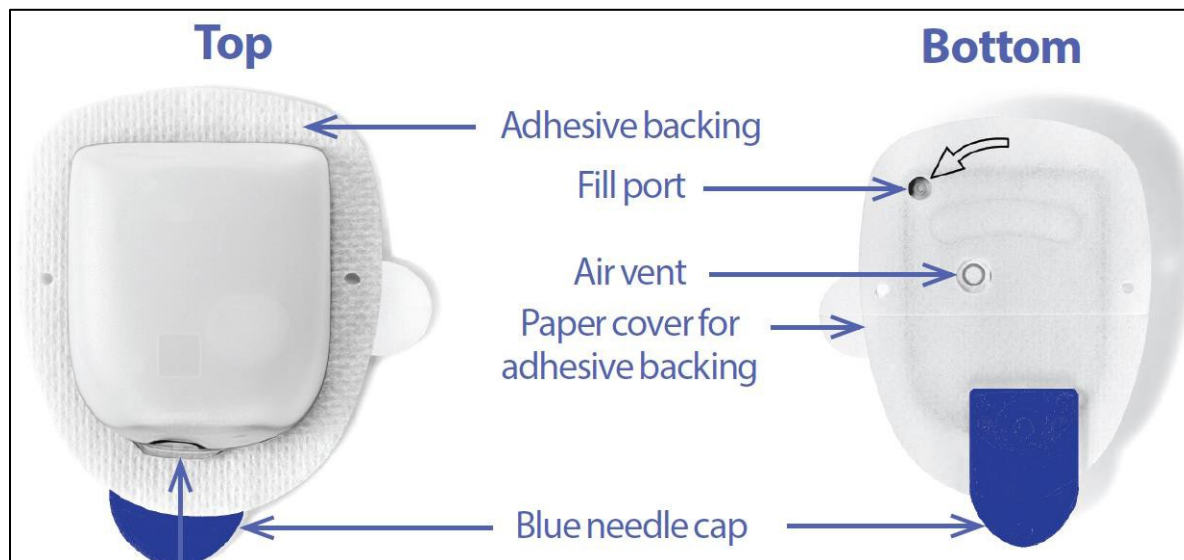859   hospitalized patients and is therefore considered experimental.

860

Figure 8: The Pod of the Omnipod5/Horizon™ ACE pump

861 ### 4.1.2 Continuous Glucose Monitoring

862 The second component of the Omnipod5/Horizon™ System is the CGM. The
863 Omnipod5/Horizon™ System will be interoperable with a compatible CGM, currently the
864 Dexcom G6 CGM System (K191450). The Pod will communicate with the Dexcom G6 via
865 Bluetooth Low Energy (BLE). Glucose values from the Dexcom transmitter will be sent to the
866 MPC algorithm residing on the Pod and will be used in insulin dosing adjustments. The glucose
867 values from the Dexcom transmitter will be sent independently to the Dexcom App on the
868 controller. The Dexcom G6 sensor is not approved for use in a hospital setting and is therefore
869 considered experimental. Alarms will be set as described in sections *3.1.3* and *3.1.4*.

870 ### 4.1.3 Horizon Data Portal

871 Data are securely uploaded from the PDM to the Insulet Cloud by cellular connection. Data are
872 then transferred from Insulet Cloud to the Horizon Data Portal (HDP), which is a platform for
873 data review and management. The HDP runs on an Amazon-based web server. The HDP will
874 provide insights including but not limited to: insulin delivery, time in range, time at each target
875 BG, automated/manual mode comparisons, and time spent in each mode.

876 The research investigators will have access to all uploaded data and be able to view historical
877 trends.

878 The Insulet Artificial Pancreas Remote Monitoring System (APRMS) allows remote monitoring
879 of glucose levels and insulin delivery in real-time, allowing remote evaluation of hospitalized
880 patients by research staff.

881 ### 4.1.4 Blood Glucose Meter and Strips

882 The point of care glucose meter approved by the hospital will be used for POC blood glucose
883 readings. The meter undergoes quality control testing and the nurses are trained on its use. The
884 specific meter used will vary by hospital.

885   **4.1.5 Study Device Accountability Procedures**

886   Device accountability procedures will be detailed in the site procedures manual.

887   **4.2 Safety Measures**

888   **4.2.1 CGM verification of validation**

889   Each new study CGM will be validated prior to use of AID. See section *3.1.1*.

890   **4.2.2 Pump Failure**

891   In the event of an early pod failure, the research staff or nursing staff trained on pod filling and
892   activation will initialize a new pod and remove the old pod. Pods will be disposed of in a
893   biohazard waste container.

894   **4.2.3 Hypoglycemia Threshold Alarm and Safety Protocol**

895   The low glucose threshold alarm setting will initially be set to 80 mg/dL, this may be adjusted by
896   the research investigators as the study progresses, or for an individual patient, but will never be
897   less than 70 mg/dL. See sections *3.1.3* and *3.1.4*.

898   **4.2.4 Hyperglycemia Threshold Alarm and Safety Protocol**

899   During the course of the study and for individual patients, researchers will be permitted to
900   change this setting within a range of 200 to 300 mg/dL. Initially this alarm will be set to 250
901   mg/dL. See sections *3.1.3* and *3.1.4*.

902   During the time period when the closed-loop system is operational and active, if a participant's
903   CGM reading is >300 mg/dL for over 1 hour or ≥400 mg/dL at any point, the following steps
904   will be taken: Ketones will be assessed at the discretion of the study physician or primary
905   hospital service for any concern about possible ketosis or DKA by drawing a serum sample
906   (beta-hydroxybutyrate) to be processed at the hospital laboratory.

Chapter 5: Testing Procedures and Questionnaires

907

5.1 Laboratory Testing

908

909 HbA1c: to be ordered after enrollment if not obtained within one month prior to admission.

910 Urine or serum pregnancy test: to be ordered after enrollment for all female enrollees of
911 childbearing potential.

912 Additional biologic samples will not be collected or ordered expressly for the purpose of this
913 study. However, certain lab results (i.e. CBC, CRP, D-dimer, or IL-6 levels) obtained during the
914 hospital admission as part of the participant's medical care will be recorded in our data
915 collection.

916 **5.2 Surveys and Questionnaires**

917 We will obtain feedback and suggestions from both the health care providers and the patients
918 who are interacting with the Omnipod5/Horizon HCL system.

919 At completion of the study, health care workers who used the system (e.g. hospitalists, nurses)
920 will be asked to complete:

921 • The 10-item System Usability questionnaire (Appendix X)
922 • A brief, 9-item questionnaire (Appendix Y) on their perceptions of using the system and
923 their suggestions for future use of the system

924 We acknowledge that the inpatient providers will be the primary interactive users with these
925 devices and also that hospitalized patients may have varying degrees of illness, and therefore
926 limited ability to participate in questionnaires. However, we believe patient input and
927 feedback is also of great potential benefit. As such, we have included patient surveys, but have
928 limited them to 8-items, to be answered if able.

929 After patients are taken off the system they will be asked to:

930 • Fill out a brief, 8-item questionnaire (Appendix Z)

Chapter 6: Unanticipated Problem, Adverse Event, and Device Issue Reporting

6.1 Unanticipated Problems

Site investigators will promptly report to the study Principal Investigator and to the Medical Monitor all unanticipated problems meeting the criteria below within seven days. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of 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 IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject 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)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

These instances must be reported to the JCHR IRB within seven calendar days of recognition. The Director of the Human Research Protection Program will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting.

6.2 Adverse Events

6.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires prolongation of current hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

967 Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or
968 any life-threatening problem or death caused by, or associated with, a device, if that effect,
969 problem, or death was not previously identified in nature, severity, or degree of incidence in the
970 investigational plan or application (including a supplementary plan or application), or any other
971 unanticipated serious problem associated with a device that relates to the rights, safety, or
972 welfare of participants (21 CFR 812.3(s)).

973 Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which
974 the device may have caused or to which the device may have contributed (Note that an Adverse
975 Event Form is to be completed in addition to a Device Deficiency or Issue Form, unless excluded
976 from reporting as defined in section *6.2*). *An event that occurs solely due to user error in which*
977 *the device functions properly generally will not be considered an ADE unless it is determined*
978 *that the instructions on the screen of the device or user manual (or similar training materials)*
979 *may have contributed to the event (note: the event may still meet criteria for reporting as an*
980 *adverse event).*

981 Device Complaints and Malfunctions: A device complication or complaint is something that
982 happens to a device or related to device performance, whereas an adverse event happens to a
983 participant. A device complaint may occur independently from an AE, or along with an AE. An
984 AE may occur without a device complaint or there may be an AE related to a device complaint.
985 A device malfunction is any failure of a device to meet its performance specifications or
986 otherwise perform as intended. Performance specifications include all claims made in the
987 labeling for the device. The intended performance of a device refers to the intended use for
988 which the device is labeled or marketed (21 CFR 803.3). Note: for reporting purposes, sites will
989 not be asked to distinguish between device complaints and malfunctions.

990 **6.2.2 Reportable Adverse Events**

991 For this protocol, a reportable adverse event includes any untoward medical occurrence that
992 meets one of the following criteria:

993 1. An ADE as defined in section *6.2.1*, unless excluded from reporting in section 8.3
994 2. An AE as defined in section *6.2.1* occurring in association with a study procedure
995 3. An AE as defined in section *6.2.1* that affects the participant's ability to complete any
996 study procedures
997 4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
998 5. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, hyperglycemia
999 or ketosis event meeting the criteria defined below.

1000 Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse
1001 events unless associated with an Adverse Device Effect. Skin reactions from sensor placement
1002 are only reportable if severe and/or required treatment.

1003 All reportable AEs—whether volunteered by the participant, discovered by study personnel
1004 during questioning, or detected through physical examination, laboratory test, or other means—
1005 will be reported on an AE form. Each AE form will be reviewed by the Medical Monitor to
1006 assess for safety and study continuation.

1007   **6.2.3 Hypoglycemic Events**

1008   Hypoglycemia not associated with an Adverse Device Effect is only reportable as an Adverse
1009   Event when either of the following parameters are met:

1010   ▪ The episode is associated with acute severe cognitive impairment, including incoherence,
1011   disorientation, and/or combativeness, seizure, or loss of consciousness. Note: If plasma
1012   glucose measurements are not available during such an event, neurological recovery
1013   attributable to the restoration of plasma glucose to normal is considered sufficient
1014   evidence that the event was induced by a low plasma glucose concentration.
1015   ▪ Capillary glucose is <40 mg/dL

1016   When a hypoglycemic event meets the above reporting requirements, a Hypoglycemia Form
1017   should be completed in addition to the Adverse Event Form. Severe hypoglycemia events should
1018   be considered to be serious adverse events with respect to reporting requirements.

1019   **6.2.4 Hyperglycemic/Ketotic Events**

1020   Hyperglycemia not associated with an Adverse Device Effect is only reportable as an Adverse
1021   Event if the event involved DKA. Hyperglycemic events are classified as DKA if the following
1022   are present:

1023   ▪ Symptoms such as polyuria, polydipsia, nausea, or vomiting;
1024   ▪ Serum ketones >1.5 mmol/L or large/moderate urine ketones;
1025   ▪ Either arterial blood pH <7.30, venous pH <7.24, or serum bicarbonate (or CO_2) <15
1026   mEq/L
1027   ▪ DKA is suspected as either the primary or a contributing cause for these findings

1028   When a hyperglycemia/ketotic event meets the above reporting requirements, an Adverse
1029   Event Form should be completed. Events meeting DKA criteria should be considered
1030   serious adverse events with respect to reporting requirements. Hyperglycemia events not
1031   meeting criteria for DKA generally will not be considered as serious adverse events
1032   unless one of the SAE criteria in section *6.2.1* is met.

1033   **6.2.5 Relationship of Adverse Event to Study Investigational Device**

1034   The study investigator will assess the relationship of any adverse event to be related or unrelated
1035   by determining if there is a reasonable possibility that the adverse event may have been caused
1036   by the study device.

1037   To ensure consistency of adverse event causality assessments, investigators should apply the
1038   following general guideline when determining whether an adverse event is related:

1039   ▪ *Unrelated*: The AE is clearly not related to a study drug/device and a likely alternative
1040   etiology exists such as an underlying disease, environmental or toxic factors or other therapy.

1041   ▪   *Unlikely Related*: The AE does not follow a reasonable temporal sequence during or after
1042   use of study drug/device and a more likely alternative etiology exists such as an underlying
1043   disease, environmental or toxic factors, or other therapy.
1044   ▪   *Possibly Related*: The AE occurred in a reasonable time during or after use of study
1045   drug/device; but could be related to another factor such as an underlying disease,
1046   environmental or toxic factors, or other therapy; and there is a possible, though weak,
1047   scientific basis for establishing a causal association between the AE and the study
1048   drug/device.
1049   ▪   *Probably Related*: The AE occurred in a reasonable time during or after use of study
1050   drug/device; is unlikely to be related to another factor such as an underlying disease,
1051   environmental or toxic factors, or other therapy; and there is a plausible, though not strong,
1052   scientific basis for establishing a causal association between the AE and the study
1053   drug/device.
1054   ▪   *Definitely Related*: The AE occurred in a reasonable time during or after use of study
1055   drug/device; cannot be explained by another factor such as an underlying disease,
1056   environmental or toxic factors, or therapy; and there is a strong scientific basis for
1057   establishing a causal association between the AE and the study drug/device.
1058   ▪   *Not Assessable*: Causality of an adverse event cannot be judged because information is
1059   insufficient or contradictory, and which cannot be supplemented or verified.

1060   **6.2.6 Severity (Intensity) of Adverse Events**

1061 The severity (intensity) of an adverse event will be rated on a three-point scale: (1) mild, (2)
1062 moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an
1063 event. Thus, a severe adverse event is not necessarily serious. For example, itching for several
1064 days may be rated as severe, but may not be clinically serious.

1065   ▪   MILD: Usually transient, requires no special treatment, and does not interfere with the
1066   participant's daily activities.

1067   ▪   MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the
1068   participant and may interfere with daily activities but is usually ameliorated by simple
1069   therapeutic measures and participant is able to continue in study.

1070   ▪   SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may
1071   cause discontinuation of study device, and generally requires systemic drug therapy or other
1072   treatment.

1073   **6.2.7 Expectedness**

1074 For a serious adverse event that is considered possibly related to study device, the Medical
1075 Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is
1076 not consistent with the risk information previously described in section *1.4*

1077   **6.2.8 Coding of Adverse Events**

1078 The Medical Monitor will review the investigator's assessment of causality and may agree or
1079 disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The

1080   Medical Monitor will have the final say in determining the causality as well as whether an event
1081   is classified as a serious adverse event and/or an unanticipated adverse device effect.

1082   **6.2.9 Outcome of Adverse Events**

1083   The outcome of each reportable adverse event will be classified by the investigator as follows:

1084   ▪ RECOVERED/RESOLVED – The participant recovered from the AE/SAE
1085   without sequelae. Record the AE/SAE stop date.
1086   ▪ RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had
1087   stabilized without change in the event anticipated. Record the AE/SAE stop date.
1088   ▪ FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the
1089   event that was the cause of death should be reported as fatal. AEs/SAEs that were
1090   ongoing at the time of death; however, were not the cause of death, will be
1091   recorded as "resolved" at the time of death.
1092   ▪ NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is
1093   defined as the event was ongoing with an undetermined outcome.
1094   An ongoing outcome will require follow-up by the site in order to determine the
1095   final outcome of the AE/SAE.
1096   The outcome of an ongoing event at the time of death that was not the cause of
1097   death, will be updated and recorded as "resolved" with the date of death recorded
1098   as the stop date.
1099   ▪ UNKNOWN – An unknown outcome is defined as an inability to access the
1100   participant or the participant's records to determine the outcome (for example, a
1101   participant that was lost to follow-up).

1102   If any reported adverse events are ongoing when a participant completes the study (or
1103   withdraws), adverse events classified UADEs will be followed until they are either resolved, or
1104   have no prospect of improvement or change, even after the participant has completed all
1105   applicable study visits/contacts. For all other adverse events, data collection will end at the time
1106   the participant completes the study. Note: participants should continue to receive appropriate
1107   medical care for an adverse event after their participation in the study ends.

1108   **6.3 Reportable Device Issues**

1109   All UADEs and ADEs as defined in section *6.2.1* will be reported on both a device issue form
1110   and AE form, except for skin reactions from CGM sensor placement or pump infusion set
1111   placement that do not require pharmacologic treatment. As noted in section *6.2.1*, events that
1112   occur due to user error generally will not require completion of a device issue form.

1113   Device complaints and device malfunctions will be reported except in the following
1114   circumstances. These occurrences are expected and will not be reported on a Device Issue Form
1115   assuming criteria for a UADE or ADE have not been met:

1116   ▪ CGM sensor lasting fewer days than expected per manufacturer

1117   ▪ CGM tape adherence issues

1118   ▪   Battery lifespan deficiency due to inadequate charging or extensive wireless communication

1119   ▪   Intermittent device component disconnections/communication failures not requiring system
1120   replacement or workaround/resolution not specified in user guide/manual.

1121   ▪   Device issues clearly addressed in the user guide manual that do not require additional
1122   troubleshooting

1123   **6.4 Timing of Event Reporting**

1124   SAEs possibly related to a study device or study participation and UADEs must be reported to
1125   the Coordinating Site (Emory University) within 24 hours of the site becoming aware of the
1126   event. This can occur via phone or email, or by completion of the online serious adverse event
1127   form and device issue form if applicable. If the form is not initially completed, it should be
1128   competed as soon as possible after there is sufficient information to evaluate the event. All other
1129   reportable ADEs and other reportable AEs should be submitted by completion on the on-line
1130   form within 7 days of the site becoming aware of the event.

1131   The Coordinating Site will notify all participating investigators of any adverse event that is
1132   serious, related, and unexpected. Notification will be made within 10 working days after the
1133   Coordinating Site becomes aware of the event.

1134   Each principal investigator is responsible for reporting serious study-related adverse events and
1135   abiding by any other reporting requirements specific to his/her Institutional Review Board or
1136   Ethics Committee. Where the JCHR IRB is the overseeing IRB, sites must report all serious,
1137   related adverse events within seven calendar days.

1138   Upon receipt of a qualifying event, the Sponsor will investigate the event to determine if a
1139   UADE is confirmed, and if indicated, report the results of the investigation to all overseeing
1140   IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per
1141   21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an
1142   unreasonable risk to participants. If so, the Medical Monitor must ensure that all investigations,
1143   or parts of investigations presenting that risk, are terminated as soon as possible but no later than
1144   5 working days after the Medical Monitor makes this determination and no later than 15 working
1145   days after first receipt notice of the UADE.

1146   Device malfunctions will be handled by the Sponsor or designee as described below. In the case
1147   of a device malfunction, information will be forwarded to Insulet by the study staff to be
1148   addressed by approved company personnel.

1149   **6.5 Safety Oversight**

1150   The study Medical Monitor will review all adverse events and adverse device events that are
1151   reported during the study. Severe adverse events (SAE) typically will be reviewed within 24
1152   hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the
1153   Medical Monitor will review compiled safety data at the end of phase 1 (n=9) and phase 2 (n=9).

1154

1155 **Safety parameter review:** assessment for any of the below attributed to sensor error or
1156 inappropriate insulin delivery by the AID system will be reviewed in aggregate after each phase.

1157 ▪ Severe hypoglycemia is defined as severe if the event required assistance of another
1158 person to actively administer carbohydrate, glucagon, or other resuscitative actions due to
1159 altered consciousness.

1160 ▪ UADE: means any serious adverse effect on health or safety or any life-threatening
1161 problem or death caused by, or associated with, a device, if that effect, problem, or death
1162 was not previously identified in nature, severity, or degree of incidence in the
1163 investigational plan or application (including a supplementary plan or application), or any
1164 other unanticipated serious problem associated with a device that relates to the rights,
1165 safety, or welfare of subjects.

1166 ▪ Diabetic Ketoacidosis (requires all four criteria to be met):

1167 (1) Symptoms such as polyuria, polydipsia, nausea, or vomiting

1168 (2) Serum ketones > 1.5 mmol/L or large/moderate urine ketones

1169 (3) Either arterial blood pH < 7.30 or venous pH < 7.24 or serum bicarbonate < 15

1170 (4) DKA is suspected as either the primary or a contributing cause for these findings

1171 The Clinical Study Director will be informed of all cases of severe hypoglycemia and DKA
1172 and the Medical Monitor's assessment of relationship to the study device; and informed of all
1173 reported device issues.

1174 **6.6 Stopping Criteria**

1175 **6.6.1 Participant Discontinuation of Study Device**

1176 In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or DKA
1177 event (or a malfunction that could have led to severe hypoglycemia or DKA), use of the HCL
1178 system will be suspended while the problem is diagnosed. The UADE will be reported to the
1179 IRB and the FDA. After assessment of the problem and any correction, use of the system will not
1180 be restarted until approval is received from the IRB and the FDA.

1181 HCL therapy will be discontinued and patients will be transitioned to standard subcutaneous
1182 insulin therapy with continued management by the primary medical/surgical team or inpatient
1183 endocrine consult service (as clinically warranted) if any of the following occur:

1184 ▪ The investigator believes it is unsafe for the participant to continue on the intervention.
1185 This could be due to the development of a new medical condition or worsening of an
1186 existing condition; or participant behavior contrary to the indications for use of the device
1187 that imposes on the participant's safety
1188 ▪ Participant's clinical team feels transition to IV insulin infusion or MDI regimen is
1189 necessary for glycemic control

1190   ▪   A successful CGM validation has not been achieved per the protocol detailed in section
1191   *3.1.1* on two consecutive CGM sensors
1192   ▪   The participant requests that the treatment be stopped
1193   ▪   Participant pregnancy
1194   ▪   Participant requires hemodialysis or continuous renal replacement therapy (CRRT)
1195   ▪   Participant requires treatment with hydroxyurea or high dose ascorbic acid
1196   ▪   One episode of DKA as defined in section *6.2.4*
1197   ▪   One episode of severe hypoglycemia as defined in section *6.2.3*
1198   ▪   One episode of DKA as defined in section *6.2.4* and one severe hypoglycemia event as
1199   defined in section *6.2.3*
1200   ▪   Participant is anticipated to be discharged from the hospital without plan to continue
1201   HCL insulin therapy in outpatient setting; transition to subcutaneous insulin regimen will
1202   be initiated prior to discharge.

1203   Transfers to the ICU will prompt discontinuation of use of the HCL component of the system
1204   (CGM may be used at described in section *3.2.1*). However, participant may be transitioned back
1205   to HCL therapy after transferring out of the ICU to a non-ICU ward based on study team
1206   assessment. ICU transfers will not be reported as AE or ADE unless the specific reason for
1207   transfer is glycemia-related (i.e. severe hypoglycemia or DKA).

1208   **6.6.2 Criteria for Suspending or Stopping Overall Study**

1209   In addition to the suspension of device use due to a UADE as described in section *6.6.1*, study
1210   activities could be similarly suspended if the manufacturer of any constituent study device
1211   requires stoppage of device use for safety reasons (e.g. product recall). The affected study
1212   activities may resume if the underlying problem can be corrected by a protocol or system
1213   modification that will not invalidate the results obtained prior to suspension.

1214   Additionally, the entire study will be placed on hold pending further review and
1215   recommendations by the Medical Monitor and IRB for any of the following:

1216   ▪   Adverse events attributable to study device (including DKA or seizure)
1217   ▪   Two patients with ≥1 episode of severe hypoglycemia attributable to insulin delivered by
1218   study device.

1219

Chapter 7: Miscellaneous Considerations

7.1 Drugs Used as Part of the Protocol

Participants will be limited to the insulin approved for pump use (i.e. insulin lispro or insulin aspart).

7.2 Collection of Medical Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

Medical Conditions during the study: In addition to conditions meeting the reporting requirements for an adverse event or device issue as described above, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (i.e., not present at the time of enrollment), and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment.

Medications: All medication for the treatment of chronic pre-existing conditions, medical conditions (including medical conditions that do not require recording), and/or adverse events that the participant is currently taking at screening and during the course of the study should be recorded. Nutraceuticals and preventative treatment also should be recorded. Medications only taken as needed will only be recorded if used during the study (e.g. Glucagon for treatment of severe hypoglycemia).

7.3 Prohibited Medications, Devices, Treatments, and Procedures

Non-insulin antihyperglycemics: non-insulin agents will be discontinued at enrollment

Additional insulins: Treatment of *hyperglycemia* with additional insulin beyond what is delivered by HCL therapy will not be permitted in conjunction with ongoing HCL use. For participants who require alternative or additional insulin therapy at the discretion of the patient's inpatient providers, the HCL system will be discontinued, as described in section *6.6.1.* Emergency use on insulins for *non-glucose-related indications*, such as hyperkalemia, are permitted; however, HCL therapy may be temporarily suspended at the discretion of the investigator and subsequently resumed as described in section *3.2.1.*

Hydroxyurea: Participants who require treatment with hydroxyurea will discontinue HCL therapy, as described in section *6.6.1.*

High-dose ascorbic acid (>1g/day): Participants who require treatment with ascorbic acid will discontinue HCL therapy, as described in section *6.6.1.*

1252 All study devices (insulin pump, CGM) must be removed before Magnetic Resonance Imaging
1253 (MRI) or diathermy treatment. CGM equipment may be worn during Computed Tomography
1254 (CT).

1255 **7.4 Precautionary Medications, Treatments, and Procedures**

1256 Acetaminophen doses of >1 gram every 6 hours may cause CGM readings to be artificially
1257 elevated. Acetaminophen use should be limited to ≤4 grams per day.

1258 **7.5 Prophylactic Medications, Treatments, and Procedures**

1259 This section is not applicable to this study.

1260 **7.6 Rescue Medications, Treatments, and Procedures**

1261 All rescue therapies are allowed at the discretion of the participant's inpatient providers. HCL
1262 therapy should be discontinued in the event that certain medications are required, as described in
1263 sections *3.2.1*, *6.6.1*, and *7.3*.

1264 **7.7 Pregnancy Reporting**

1265 Pregnancy occurring during this study is highly unlikely. However, if pregnancy is discovered
1266 after enrollment, the participant will be discontinued from the study. The occurrence of
1267 pregnancy will be reported to the Coordinating Site within seven days and to the JCHR IRB as
1268 an Unanticipated Problem within seven calendar days.

1269 **7.8 Participant Compensation**

1270 Participant compensation will be specified in the informed consent form.

1271 **7.9 Participant Withdrawal**

1272 Participation in the study is voluntary, and a participant may withdraw at any time. For
1273 participants who withdraw, their data will be used up until the time of withdrawal.

1274 **7.10 Confidentiality**

1275 For security and confidentiality purposes, participants will be assigned an identifier that will be
1276 used instead of their name. Protected health information gathered for this study will be shared
1277 with the Statistical Center, the Jaeb Center for Health Research in Tampa, FL. De-identified
1278 participant information may also be provided to research sites involved in the study.

Chapter 8: Statistical Considerations

8.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below.

8.2 Statistical Hypotheses

This is a pilot and feasibility trial and is not powered to reach statistical conclusions.

8.3 Sample Size

The sample size was a convenient sample size by which to obtain preliminary data on implementing the HCL/AID system in a hospital setting. The maximum number of participants to be consented for participation in this study (n=30) is based upon the goal of enrolling 18 patients with at least 48 hours of data during HCL therapy and to account for the potential for early device wear termination, ICU transfer, or early discharge.

8.4 Outcome Measures

Primary Endpoints:

Aim 1: Proportion of time spent in HCL after CGM validation

Aim 2: Percentage of time sensor glucose is within target glucose range [time-in-range (TIR)], defined as sensor glucose 70-180 mg/dL.

Secondary Endpoints:

Aim 1.1: System function

- Time from enrollment to start of HCL therapy
- Percent of time with CGM readings
- Percentage of validations that were successful
- Number of CGM readings within %15/15 of POC readings and within %20/20 of POC readings with the cut point at 70 mg/dL.

Aim 1.2: Implementation processes and adoptability of inpatient HCL therapy by clinical staff and patients (Qualitative analyses)

- Patient and Providers: Open-ended feedback
- Patient and Providers: Survey questionnaire results

Aim 2.1: Glycemic control

1308 ▪ Number of hypoglycemic (<70 mg/dL) and clinically-important hypoglycemic (<54
1309 mg/dL) episodes per patient and per patient-day
1310 ▪ Percent time below range (TBR, <70mg/dL)
1311 ▪ Percent time in clinically-important hypoglycema(<54 mg/dL)
1312 ▪ Percent time above range (TAR, >180 mg/dL)
1313 ▪ Percent time in severe hyperglycemia (>250 mg/dL)
1314 ▪ Glycemic variability (CV and SD)

1315 **Aim 2.2:** HCL Settings

1316 ▪ Frequency of setting adjustments for clinically-important hypoglycemia (<54
1317 mg/dL): Overall, to basal rate, to ICR, to ISF
1318 ▪ Frequency of setting adjustments for prolonged severe hyperglycemia (>250
1319 mg/dL for >1 hour), Overall, to basal rate, to ICR, to ISF
1320 ▪ Insulin requirements: Total daily insulin (TDI), Total daily basal insulin, Total
1321 daily bolus insulin

1322 **8.5 Analysis Dataset**

1323 All relevant participant data will be included in the analysis of a single data set for this feasibility
1324 study.

1325 **8.6 Analysis of the Primary Efficacy Endpoint(s)**

1326 The primary purpose of this pilot study is to assess the feasibility HCL use in the inpatient
1327 setting; therefore, no formal power calculations were performed. The main objectives of this
1328 study are to improve the quality and efficiency of the main study. In addition, it is conducted in
1329 order increase the investigators' experience with the technology in a different setting. We will
1330 list values for each patient as well as provide summary statistics appropriate to the distribution.
1331 To determine the operability of AID in the hospital (Aim 1) we will calculate the proportion of
1332 time spent in HCL after CGM sensor values meet validation criteria [sensor glucose values are
1333 within ±20% of POC values for glucose levels ≥70 mg/dL or ±20 mg/dL for POC glucose values
1334 <70 mg/dL]. To evaluate glycemic control (Aim 2) we will determine the percentage of time
1335 sensor glucose values are within target glucose range [time-in-range (TIR); 70-180 mg/dL],
1336 during closed-loop insulin delivery.

1337 **8.7 Analysis of the Secondary Endpoints**

1338 The analysis of secondary endpoints will parallel that described above for the primary analysis
1339 with summary statistics given for each of the metrics listed in Section 8.4

1340 **8.8 Safety Analyses**

1341 Safety endpoints will be analyzed using summary statistics during treatment. AEs will be coded
1342 as described in section 6.2.8. Severity and relationship of AE to study agent will be determined
1343 as described in section 6.2. The event start date, stop date, severity, relationship, outcome, and

1344 duration will also be recorded. The Medical Monitor will conduct a review of safety parameters
1345 at the end of each study phase, as described in Section 6.5.

1346 The following will be tabulated during the feasibility study:

1347 • Number of adverse events
1348 • Number of participants with at least one event
1349 • Number of serious adverse events
1350 • Number of participants with at least one serious adverse event
1351 • Number of unexpected device events
1352 • Number of unexpected serious device events
1353 • Number of ICU transfers
1354 • Number of adverse events thought by investigator to be related to study device
1355 • Number of participants who stopped the intervention in response to an adverse
1356 event
1357 • Number of severe hypoglycemic events as defined in the protocol
1358 • Number of severe hypoglycemic events associated with seizure or loss of
1359 consciousness
1360 • Number of diabetic ketoacidosis events as defined in the protocol

1361 **8.9 Intervention Adherence**

1362 The adherence to the protocol will be determined by daily use of HCL after enrollment and will
1363 be calculated from time of enrollment to ICU transfer or hospital discharge. We will obtain
1364 preliminary estimates about the frequency and reasons for discontinuation of the intervention
1365 during this feasibility study.

1366 **8.10 Protocol Adherence and Retention**

1367 Potential study subjects will be identified and pre-screened among non-ICU patients with
1368 hyperglycemia requiring insulin therapy. Strategies to address potential problems with
1369 recruitment will include bi-weekly communications with Drs. Pasquel, Davis, Buckingham, Lal,
1370 and Brown.

1371 A study coordinator or investigator will conduct informed consent in eligible subjects prior to
1372 any study procedures. Screening and recruitment reports will be generated monthly that include
1373 actual and expected recruitment statistics. Based on preliminary studies with inpatient use of
1374 CGM we expect to retain most patients in this study.

1375 **8.11 Baseline Descriptive Statistics**

1376 Baseline characteristics will be collected and reported for all participants in this feasibility study.

1377 **8.12 Device Issues**

1378 Any technical issues will be reported to Insulet Corporation. Any device issues affecting patient
1379 care will be reported as below and reviewed by the Medical Monitor.

1380 **8.13 Planned Interim Analyses**

1381 The criteria below will be considered events prompting an interim review and safety analysis
1382 prior to continuation of the study. The study investigators and statisticians will perform the
1383 statistical analysis that will be reviewed by the Medical Monitor. There are no blinding
1384 procedures to be addressed in this feasibility study.
1385 ▪ Adverse events attributable to study device (including DKA or seizure)
1386 ▪ Two patients with ≥1 episode of severe hypoglycemia attributable to insulin delivered by
1387 study device.

1388 **8.14 Sub-Group Analyses**

1389 Not applicable in this feasibility study.

1390 **8.15 Multiple Comparison/Multiplicity**

1391 Not applicable in this single-arm feasibility study.

1392 **8.16 Exploratory Analyses**

1393 No additional exploratory analyses are planned.

1394 **8.17 Additional Tabulations and Analyses**
1395 Not applicable in this single-arm feasibility study.

Chapter 9: Data Collection and Monitoring

9.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g. lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.)

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation.

9.2 Study Records Retention

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Study documents should be retained for a minimum of 3 years after final reporting. 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 sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.3 Quality Assurance and Monitoring

Designated personnel from Emory University will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote

1432 monitoring will be performed in real-time with on-site monitoring performed to evaluate the
1433 verity and completeness of the key site data. Elements of the RBM may include:

1434 • Qualification assessment, training, and certification for sites and site personnel
1435 • Oversight of Institutional Review Board (IRB) coverage and informed consent
1436 procedures
1437 • Central (remote) data monitoring: validation of data entry, data edits/audit trail,
1438 protocol review of entered data and edits, statistical monitoring, study closeout
1439 • On-site monitoring (site visits): source data verification, site visit report
1440 • Agent/Device accountability
1441 • Communications with site staff
1442 • Patient retention and visit completion
1443 • Quality control reports
1444 • Management of noncompliance
1445 • Documenting monitoring activities
1446 • Adverse event reporting and monitoring

1447 Coordinating Site (Emory University) representatives or their designees may visit the study
1448 facilities at any time in order to maintain current and personal knowledge of the study through
1449 review of the records, comparison with source documents, observation and discussion of the
1450 conduct and progress of the study. The investigational site will provide direct access to all trial
1451 related sites, source data/documents, and reports for the purpose of monitoring and auditing by
1452 the sponsor, and inspection by local and regulatory authorities.

1453 **9.4 Protocol Deviations**

1454 A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure
1455 requirements. The noncompliance may be either on the part of the participant, the investigator,
1456 or the study site staff. As a result of deviations, corrective actions are to be developed by the site
1457 and implemented promptly.

1458 The site PI/study staff is responsible for knowing and adhering to their IRB requirements.
1459 Further details about the handling of protocol deviations will be included in the monitoring plan.

1460 # Chapter 10: Ethics/Protection of Human Participants

1461 ## 10.1 Ethical Standard

1462 The investigator will ensure that this study is conducted in full conformity with Regulations for
1463 the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50,
1464 21 CFR Part 56, and/or the ICH E6.

1465 ## 10.2 Institutional Review Boards

1466 The protocol, informed consent form(s), recruitment materials, and all participant materials will
1467 be submitted to the IRB for review and approval. Approval of both the protocol and the consent
1468 form must be obtained before any participant is enrolled. Any amendment to the protocol will
1469 require review and approval by the IRB before the changes are implemented to the study. All
1470 changes to the consent form will be IRB approved; a determination will be made regarding
1471 whether previously consented participants need to be re-consented.

1472 ## 10.3 Informed Consent Process

1473 ### 10.3.1 Consent Procedures and Documentation

1474 Informed consent is a process that is initiated prior to the individual's agreeing to participate in
1475 the study and continues throughout the individual's study participation. Extensive discussion of
1476 risks and possible benefits of participation will be provided to the participants and their families.
1477 Consent forms will be IRB-approved and the participant will be asked to read and review the
1478 document. The investigator will explain the research study to the participant and answer any
1479 questions that may arise. All participants will receive a verbal explanation in terms suited to their
1480 comprehension of the purposes, procedures, and potential risks of the study and of their rights as
1481 research participants. Participants will have the opportunity to carefully review the written
1482 consent form and ask questions prior to signing.

1483 The participants should have the opportunity to discuss the study with their surrogates or think
1484 about it prior to agreeing to participate. The participant will sign the informed consent document
1485 prior to any procedures being done specifically for the study. The participants may withdraw
1486 consent at any time throughout the course of the trial. A copy of the informed consent document
1487 will be given to the participants for their records. The rights and welfare of the participants will
1488 be protected by emphasizing to them that the quality of their medical care will not be adversely
1489 affected if they decline to participate in this study.

1490 ### 10.3.2 Participant and Data Confidentiality

1491 Participant confidentiality is strictly held in trust by the participating investigators, their staff,
1492 and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological
1493 samples and genetic tests in addition to the clinical information relating to participants.
1494 Therefore, the study protocol, documentation, data, and all other information generated will be
1495 held in strict confidence. No information concerning the study or the data will be released to any
1496 unauthorized third party without prior written approval of the sponsor.

1497   The study monitor, other authorized representatives of the sponsor, representatives of the IRB,
1498   regulatory agencies or company supplying study product may inspect all documents and records
1499   required to be maintained by the investigator, including but not limited to, medical records
1500   (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical
1501   study site will permit access to such records.

1502   The study participant's contact information will be securely stored at each clinical site for
1503   internal use during the study. At the end of the study, all records will continue to be kept in a
1504   secure location for as long a period as dictated by the reviewing IRB, institutional policies, or
1505   sponsor requirements.

1506   Study participant research data, which is for purposes of statistical analysis and scientific
1507   reporting, will be transmitted to and stored at the Coordinating Site and Statistical Center. This
1508   will not include the participant's contact or identifying information, unless otherwise specified in
1509   the informed consent form. Rather, individual participants and their research data will be
1510   identified by a unique study identification number. The study data entry and study management
1511   systems used by clinical sites will be secured and password protected. At the end of the study, all
1512   study databases will be de-identified and archived.

1513   ### 10.3.3 Future Use of Stored Specimens and Data

1514   Biologic samples from participants will not be stored for the purposes of this study. Genetic
1515   testing will not be performed as part of this study.

Chapter 11: References

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