UVA CENTER FOR DIABETES TECHNOLOGY

Adapting Diabetes Treatment Expert Systems to Patient's Expectations and Psychobehavioral Characteristics in Type 1 Diabetes

Protocol Chair

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KEY ROLES

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PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0			24-Apr-2020	Original Protocol
1.1	Mary Oliveri	Mary Oliveri	20-May-2020	Added • Demographic Data Survey added at screening
1.2	Mary Oliveri		03-Aug-2020	Full Board Revisions: • Clarified that participants may contact the study team at any time during the study to report adverse events (Section 5.1.1 5.3.2, 6.4.3, 6.6.3, 7.6.3). • Corrected erroneous sentence referencing DHHS 46.405 (section 10.3). • Corrected bullet formatting (section 12.3.2). • Removed references to Medical Monitor throughout protocol. • Added references to Data Safety Monitoring Board (section 12.10).
1.3	Jon Olson	Mary Oliveri	08-Nov-2020	Study Team modifications: • Physical examination (may use a medical record within the past 6 months) • Weight, height (participant may self-report this information) • Vital signs including measurement of blood pressure and pulse (may use a medical record within the past 6 months) • Participants will have the option to be given a receiver from the study team for medical needs.
1.4	Jon Olson	Mary Oliveri	22-Jan-2021	DSMB Request: • If applicable, subjects will have a pregnancy test between phases (section 6.4).
2.0	Mary Oliveri	Marc Breton, Ralf Nass	05-Oct-2021	Study Team Modifications: • Modified HbA1c limit to HbA1c 6.0-11.0%, inclusive (section 3.3)Edited Sensor Augmented Pump Therapy (SAP) to Sensor

				Augmented Mode (SAM) throughout the document • Deleted inclusion of carbohydrate counting (section 3.3) • Added NPH insulin as study exclusion (section 3.4) • Added Post-Screening Assessment section describing participant requirements (section 3.5) • Clarified Training visit definition (Chapter 4)Clarified pump and MDI training issues (section 4.1.2, 4.1.3) • Study physician may add up to two weeks to CGM run-in period (section 5.2.1) • Revised Figure 4 and Figure 5

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Adapting Diabetes Treatment Expert Systems to Patient's Expectations and Psychobehavioral Characteristics in Type 1 Diabetes

Protocol Version/Date: v2.0/05-Oct-2021

I have written 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. 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: 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).

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: _____ / _____ / _____

Investigator's Name: _____

Site Name: University of Virginia

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
API	Application Programming Interface
ATI	Acceptance and Trust Index
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CR	Carbohydrate Ratio
CLC	Closed-Loop Control
CGM	Continuous Glucose Monitor
CSII	Continuous Subcutaneous Insulin Injection
CV	Coefficient of Variation
DiAs	Diabetes Assistant
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DSS	Decision Support System
DWM	DiAs Web Monitoring
eA1c	Estimated Hemoglobin A1c
EMA	Ecological Momentary Assessment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	General Linear Models
GV	Glucose Variability
HbA1c	Hemoglobin A1c
HBGI	High Blood Glucose Index
HTTP	Hypertext Transfer Protocol
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
ISF	Insulin Sensitivity Factor
JSON	JavaScript Object Notation
LBGI	Low Blood Glucose Index
NIH	National Institutes of Health
PF	Personalized Feedback
POC	Point-of-Care

QC	Quality Control
QOL	Quality of Life
REST-ful	Representational State Transfer
SAM	Sensor Augmented Mode
SAP	Sensor-Augmented Pump therapy
SH	Severe Hypoglycemia
SI	Insulin Sensitivity
SMBG	Self-Monitoring of Blood Glucose
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UI	User Interface
URL	Uniform Resource Locator
XML	Extensible Markup Language

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Adapting Diabetes Treatment Expert Systems to Patient's Expectations and Psychobehavioral Characteristics in Type 1 Diabetes
Investigational Device	CGM-based Personalized Feedback (PF) and Decision Support System (DSS)
Objectives	**Aim 1** (control of GV) We will confirm and contrast the efficacy of two previously designed technological interventions – Personalized Feedback (PF) and Decision Support System (DSS) - in reducing glucose variability (GV) in Type 1 Diabetes Mellitus (T1DM) during a 6-month randomized crossover clinical trial. **Aim 2** (personalization of treatment policy) We hypothesize that the participants in this study will have technology intervention preferences (e.g. PF or DSS) that can be predicted by key psychosocial and behavioral parameters and are prognostic of the level of GV control achievable by the intervention. **Aim 3** (monitoring of treatment policy) Finally, we propose to define a novel, measurable, technology Acceptance and Trust Index (ATI), passively observing and recording user-system interactions, and validate this new index using active Ecological Momentary Assessment (EMA) to track user subjective response to DSS.
Study Design	This is a randomized crossover study in T1DM adults designed to demonstrate the efficacy of personalized feedback (PF) and decision support (DSS) over sensor-augmented mode (SAM) therapy and to establish relationships between the level of glucose variability (GV) control achievable by the intervention and individual psycho-behavioral characteristics.
Number of Sites	1
Outcomes	A key advantage of the proposed study design (beyond the optimal statistical power) is the possibility to explore the glucose control and psycho-behavioral impact of features being added and/or enhanced with prescriptive components (DSS), vs. features being limited to information (PF) or even removed (SAM).
Population	Key Inclusion Criteria • Age 18 years and older • T1DM diagnosis for at least 1 year • Established insulin parameters Key Exclusion Criteria d • Hemoglobin A1c 6.0-11.0%, inclusive
Sample Size	Enrollment will proceed with the goal of completing 4 cohorts of about 25 participants each (expected retention 20 per cohort)
Treatment Groups	• De-escalation (DSS→PF→SAM) • Escalation (SAM→PF→DSS)
Participant Duration	The study duration for each participant is approximately 7 months.
Protocol Overview/Synopsis	Four cohorts of about 25 participants each (expected retention 20 per cohort). Each cohort will continue for ~7 months. Following recruitment, screening, and a run-in period of SAM, participants will be randomized into one of two groups: escalation vs. de-escalation of devices and function. Each treatment modality (SAM, PF, DSS) will continue for about 8 weeks, with the last 4 weeks used to assess GV from CGM data.

STUDY VISITS AND PROCEDURES SCHEDULE

	Visit 1 Screening and Questionnaires	Visit 2 Study Device and Procedures Training	SAM Run-in	Visit 3 Eligibility Assessment, Randomization and Training	DiAs Use in Phase 1 Mode	Visit 4 Phase 2 Initiation	DiAs Use in Phase 2 Mode	Visit 5 Phase 3 Initiation	DiAs Use in Phase 3 Mode	Visit 6 Study Exit	Visit 7 Post Study Check in
Location	Clinic	Clinic	Home x 2-4 weeks	Web Conference or Clinic	Home x 8 weeks	Web Conference or Clinic	Home x 8 weeks	Web Conference or Clinic	Home x 8 weeks	Phone or Clinic	Phone or Clinic
Informed Consent	X										
Medical History	X										
Medications	X										
Physical Exam (including vital signs, height/weight)	X										
Pregnancy Test (if childbearing potential)	X					X		X			
Blood Testing: TSH, CMP (additional labs as necessary)	X										
Questionnaires	X		X	X	X	X	X	X	X	X	
Equipment Training		X									
DiAs in SAM Training		X									
Glycemic Treatment Guidelines Training		X									
Glucagon Emergency Kit Training		X									
Use of DiAs in SAM			X								
Eligibility Assessment				X							
AE Assessment				X		X		X		X	
Randomization				X							
DiAs Phase 1 Mode Training				X							
EMA Training				X							

	Visit 1 Screening and Questionnaires Visit 1 Screening and Questionnaires	Visit 2 Study Device and Procedures Training Visit 2 Study Device and Procedures Training	SAM Run-in SAM Run-in	Visit 3 Eligibility Assessment, Randomization and Training Visit 3 Eligibility Assessment, Randomization and Training	DiAs Use in Phase 1 Mode DiAs Use in Phase 1 Mode	Visit 4 Phase 2 Initiation Visit 4 Phase 2 Initiation	DiAs Use in Phase 2 Mode DiAs Use in Phase 2 Mode	Visit 5 Phase 3 Initiation Visit 5 Phase 3 Initiation	DiAs Use in Phase 3 Mode DiAs Use in Phase 3 Mode	Visit 6 Study Exit Visit 6 Study Exit	Visit 7 Post Study Check in Visit 7 Post Study Check in
Location	Clinic	Clinic	Home x 2-4 weeks	Web Conference or Clinic	Home x 8 weeks	Web Conference or Clinic	Home x 8 weeks	Web Conference or Clinic	Home x 8 weeks	Phone or Clinic	Phone or Clinic
Use of DiAs in Phase 1 Mode					X						
EMA Surveys					X		X		X		
DiAs Phase 2 Mode Training						X					
Use of DiAs in Phase 2 Mode							X				
DiAs Phase 3 Mode Training								X			
Use of DiAs in Phase 3 Mode									X		
Review diabetes management & AEs				X		X		X		X	X

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Chapter 1 Background

1.1. Introduction

1.1.1. Significance

Type 1 diabetes mellitus (T1DM) is an autoimmune condition resulting in absolute insulin deficiency and a life-long need for insulin replacement [1]. Glycemic control in T1DM remains a challenge, despite the availability of modern insulin analogs [2], the improving accuracy of glucose monitoring [3-4], and the widening use of intensive insulin therapy. While new technologies have proven benefits in avoiding diabetes related complications [5] and may have reduced excess mortality in some populations [6], excess mortality and complication rates remain significantly higher in T1DM when compared to the general population [7-8].

Glucose variability (GV) in T1DM is typically at the root of clinicians' inability to safely achieve near-normal average glycemia, as reflected by hemoglobin A1c (HbA1c) [9]. While target HbA1c values of 7% or less result in decreased risk of micro- and macrovascular complications [10-13], the risk for severe hypoglycemia (SH) increases with tightening glycemic control [14-16]. Consequently, hypoglycemia has been implicated as the primary barrier to optimal control [17-18]. Thus, individuals with T1DM face a life-long optimization challenge: reduce average glucose levels and postprandial hyperglycemia while simultaneously avoiding hypoglycemia. A strategy for achieving such an optimization can only be effective if it reduces GV. This is because bringing average glycemia down is only possible if GV is constrained – otherwise blood glucose (BG) fluctuations would inevitably enter the range of hypoglycemia. However, averages and HbA1c fail to capture GV and the attendant risks associated with extremes of hypo- and hyperglycemia. Indeed, in addition to establishing HbA1c as the gold standard for average glycemic control, the Diabetes Control and Complications Trial (DCCT) concluded that: "HbA1c is not the most complete expression of the degree of glycemia. Other features of diabetic glucose control, which are not reflected by HbA1c, may add to, or modify the risk of complications. For example, "the risk of complications may be highly dependent on the extent of postprandial glycemic excursions" [19]. Thus, more recent studies increasingly focused on the variability of BG fluctuations as an independent risk factor for diabetes complications [9, 20-21], particularly cardiovascular disease [22-25].

Intensive insulin therapy: Introduced in the 1980s, intensive insulin treatment by multiple daily injections (MDI) or use of continuous subcutaneous insulin infusion (CSII), typically includes basal insulin administered to cover the overnight and fasting periods and bolus insulin given with meals to cover carbohydrate consumption and to correct postprandial hyperglycemia, in an attempt to mimic insulin secretion in health [26]. Advanced insulin therapy relies on key individual parameters such as basal rate, carbohydrate ratio (CR) and insulin sensitivity factor (ISF) [26]. Evidence-based resources are available to patients to control their insulin intake and schedules, and clinicians to initiate and maintain CSII therapy by selecting appropriate basal rates, carbohydrate ratios, and insulin sensitivity factor patterns [27].

Expert systems and Control of Glucose Variability: Periodic adjustments of basal rate, CR, and ISF patterns are needed based on review of self-monitoring blood glucose (SMBG) profiles, or continuous glucose monitoring (CGM). If a pattern is identified, optimized insulin dosing parameters are calculated and implemented. This can be a time-consuming and onerous task, requiring data to be downloaded from multiple devices and often subjectively evaluated. Information technology is increasingly playing a positive role in improving the management of chronic conditions [28-29], including diabetes [30]. For example, in T1DM, telemedicine and online patient support has shown promising results [31-32]; and retrospectively linking behavior to glycemic outcomes has proven effective as well [33]. With improvements in SMBG and CGM technologies, a growing appreciation of the quantitative (algorithmic) aspect of the management of T1DM has led to new tools for remote patient monitoring, data aggregation and visualization [34]. Early research has developed algorithms for titrating individual insulin treatment parameters, including iterative learning approaches such as 'run-to-run' with structured SMBG [35-39]. Insulin titration and dosing tools for type 2 diabetes are beginning to enter the marketplace [40], mostly using SMBG. Today, researchers are actively working on CGM-based decision support for T1DM [26, 41-44], capable of providing specific feedback to the clinician regarding suggested therapy changes. These expert systems have the potential to streamline clinic visits and facilitate collaborative patient-centered interactions, but in their most advanced form, they deliver advice directly to the patient [41], reducing burden and uncertainty when making self-management decisions.

Automated Insulin Delivery: Closed loop control (CLC) technology (i.e. artificial pancreas or AP), involves the pairing of CGM with CSII (insulin pump) via a closed loop control algorithm which automatically adjusts insulin infusion in real-time [45]. In the past decade, AP studies have advanced from short-term inpatient studies [46], to long-term clinical trials in free-living conditions using wearable wireless automated AP systems [47]. Our AP studies have enrolled >450 T1DM patients, who used our smartphone-based system for over 280,000 hours.

Algorithmic advances and computational platforms from these efforts are at the core of this investigation.

Smartphone based data acquisition and advice delivery platforms: This investigation brings together two key pieces of mobile technology to advance T1DM treatment: The Diabetes Assistant (DiAs) and Ecological Momentary Assessment (EMA).

Diabetes Assistant (DiAs): The Diabetes Assistant (DiAs) [48-49] platform is a smartphone-based, modular, portable device developed at the University of Virginia (UVa), in collaboration with the University of Montpellier (Figure 1). DiAs operates on a commercial phone, using a specifically modified Android operating system, to enable wireless communication with satellite devices like insulin pumps, CGMs, and any medical device using a standard wireless protocol like BT or BTLE. Its modular architecture allows different control modules to be swapped in real time, enabling either automated control (CLC) or expert-decision support systems. The DiAs platform also integrates automated data transfer to a secured server, enabling cloud functionalities such as remote monitoring and patient specific adaptation of treatment [50]. DiAs is filed with the FDA (MAF 2109) and has been approved for use by adults, adolescents, and children with T1DM in over 20 clinical trials. DiAs is a powerful computation platform that enables both local control of insulin and cloud applications; it is the most advanced research glucose control platform to date and has been deployed for months in home CLC trials. DiAs enables the seamless integration and sequential development of modular decision support systems in a form factor assessed by focus groups to be acceptable by people with T1DM.

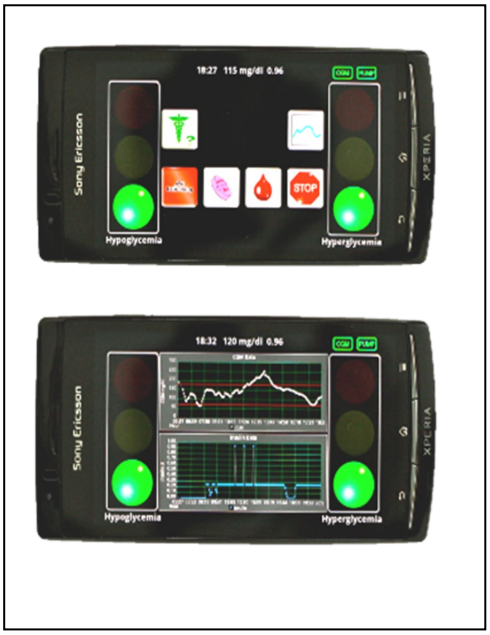

Figure 1: The DiAs system, a mobile Glucose control platform

Leveraging EMA to assess user's subjective reactions to the decision support system will enable the first study with such detailed and dynamic investigation of daily trust levels, psychological, and behavioral responses.

Remote computation and cloud analytics: DiAs is capable of real-time data transmission to secure remote servers: the DiAs Web Monitoring (DWM) is a suite of functionalities located on a secure server within the UVA Health System network. At its core is a database that receives real-time data about the DiAs status, such as CGM, insulin delivered, connectivity status, and algorithm status. The system is equipped with a dedicated interface to allow for third party applications to

access data stored on the DWM server. It relies on the HTTP protocol and a Representational State Transfer (REST-ful) architecture to provide authenticated users with access to the content of the database, formatted as JSON or XML. The API uses a URL-based system of requests to target and filter the data sent to the client. Several systems are already connected to DWM [50-52].

Impact of technology trust and acceptance in glycemic control: Trust must be earned; it cannot be assumed. The concept of trust plays an important role in an individual's willingness to engage in the use of a medical device. In its basic definition 'trust is to depend or rely on another' [53]. The "other" can be another person or a device. Trust and acceptance incorporate several key constructs i.e. confidence versus fear, satisfaction versus burden, distress versus improved quality of life. Additional factors include perceived usefulness, cost-benefit balance, perceived ease of use, or impact on others as well as oneself (positive and negative) [54-55].

Human factors research indicates that such psychosocial variables play an important role when it comes to technology uptake. In CGM, factors predictive of uptake and effectiveness, include perceived system reliability and ease-of-use [53,56]. Prior CLC research has also shown that clinical trials participants were quick to trust a novel device (CGM, CSII and algorithm), sacrificing personal control over diabetes management to the system, whilst a negative experience impeded trust, contributing to discontinued use. Other studies of CLC systems have found that, when users lack trust, they tend to override the devices, while users who report trust in the system experience decreases in diabetes burden and stress [57]. In general, trust is associated with positive glycemic outcomes and improved psychosocial functioning and quality of life (QOL) [58]. Barriers to trust and continued acceptance include frustration felt when expectations of the system are not met; feelings of being overwhelmed by the amount of information provided, or negative reactions from the social environment e.g. diabetes-related stigma, possibly resulting in a perceived need to explain/justify why a technical device is worn constantly on the body [53]. In addition to patients' perceptions rooted in their previous experience, unrealistic expectations may lead to disappointment and discontinuation of the device.

General 'tech savviness' can also play a role in acceptance in that those more familiar and comfortable with technology may be more willing to trust the system. Furthermore, the time and effort required to invest in building device-related skills, trust and acceptance may be underestimated (and often is), as these range from technical handling to integrating the system information into one's diabetes self-management and everyday living without intrusive disruptions. Therefore, psychological and behavioral factors play a critical role in the acceptance of diabetes technologies and the trust patients put in them. It is crucial to determine the psychosocial and behavioral predictors to uptake and continued use of technology in order to aid

identification of those individuals most likely to realize benefits of any intervention as well as those individuals who may require more support to succeed with technology. Additional individual patient's characteristics (e.g. diabetes belief systems and self-management skills) may be predictive of technology acceptance, trust, use, and benefit. At present, little is known about psychological, behavioral and social factors that contribute to diabetes technology adoption and successful use.

This investigation will determine psychosocial and behavioral predictors of intervention efficacy, providing data and psychological techniques to support future onboarding and successful use of the DSS, as well as validate novel mechanisms to track trust and acceptance, allowing future systems to adapt to the user's needs, minimizing potential burden and lifestyle interference, and ensuing individualized, person-centered support for optimal glycemic and psychosocial/quality of life outcomes.

Hypothesis: We hypothesize that psycho-behavioral factors are likely to influence system acceptance and trust, and ultimately the patients' success in leveraging the device to achieve their individual goals, e.g. better glycemic control with similar burden, or lower treatment burden with similar glycemic control. To our knowledge, no technological intervention has been assessed in terms of which mode of advice or information delivery is most appropriate to a patient's unique characteristics. Thus, the proposed study is the first to map key psycho-behavioral factors to the expert system characteristics that are most beneficial for treatment success.

Tracking and Quantifying User/System Interactions: This study merges the expert platform (DiAs) with software designed to detect, record, and contextualize the interactions between the patient and a medical device. This unique combination of established mobile diabetes technology and cutting-edge software previously unrelated to diabetes, will allow: (i) systematically record treatment behaviors; (ii) track user/system interactions, and (iii) accurately quantify the resulting glucose control. The new DiAs-EMA system is a key innovation and a new tool enabling us to study the interplay of technology, behavior, and treatment of diabetes.

Using a tracking system, the investigators will be able to observe each user of the system; this in turn allows for an internal quantification of the user level of trust and acceptance and its time course.

Modular Design of Decision Support Systems: The AP and diabetes expert systems are assembled from independent (but compatible) modules, each performing a specific control or diagnostic function, e.g. prevention of hypoglycemia or postprandial insulin corrections [59-60]. This architecture allowed for sequential testing and clinical deployment of AP and DSS components and provided a structured framework for networks of control systems [60]. This

architecture is fundamental to the goals of this project: we plan to further refine and evaluate a layered glucose variability control system activating different modules depending on the stage of the proposed study (PF vs DSS). Moreover, a modular system is inherently capable of graceful degradation-the capacity to ensure safety even if a module fails. Eventually, this architecture would allow the system to adapt its function to maximize system use and adherence, sequentially enabling more advanced functions as patients build trust and integrate DSS in their treatment. The modules to be included in the PF and DSS have been validated in human clinical trials (see 1.1.2 Preliminary Data). These modules include:

- **CGM value, trace, and threshold alarms (applicable to SAM & PF & DSS):** Similar to commercial real-time CGM (e.g. Dexcom G6), this module informs the user of the current glucose level and how it has changed recently, enabling treatment decisions. Alerts are set by the user to trigger if BG leaves a preset range.
- **Hypoglycemia Risk Indicator (PF & DSS):** Based on our group's work in the 1990s and the definition of the glycemic risk ranges [61], we have developed short (1-3 hours), medium (1-3 days), and long (1-3 weeks) term hypoglycemia risk indices. Prototypes of these modules have been evaluated clinically (see Preliminary Data).
- **Insulin Sensitivity Profile & Indicator (PF & DSS):** We have designed an algorithm capable of tracking changes in insulin sensitivity (SI) and creating daily and monthly SI profiles [62]. We additionally validated a real-time SI indicator to inform insulin dosing (e.g. is the patient more or less sensitive than usual?) [41].
- **Insulin on Board (PF & DSS):** IOB is a key index to avoid insulin stacking and is available to DiAs through its insulin pump connectivity. DiAs uses a common 4-6 hours action curve derived from encoparesis study [63].
- **Exercise Advice (DSS):** From our modeling work [64], we have derived an advisory module that ensures safety of mild to moderate exercise by predicting whether an exercise bout is likely to result in hypoglycemia and providing a graded carbohydrate supplementation strategy. See clinical validation in [64].
- **Bedtime Advice (DSS):** Similar to the Exercise advisor, this module uses logistic regression and recent data (CGM, insulin and meals) to gauge overnight hypoglycemia risk and provide bedtime carbohydrate advice.
- **Smart Bolus Calculator (DSS):** DSS supports advanced bolus calculation capable of accounting for several GV factors such as metabolic characteristics (correction based on 45 min predicted glucose to account for insulin delays) and SI fluctuations (insulin sensitivity tracker).
- **Automated Treatment Parameter Optimization (DSS):** Based on replay simulation technology [42], this optimization routine analyzes the previous 30 days of CGM, insulin, and meal data to provide updated insulin treatment parameters (CR, ISF).

1.1.2. Preliminary Data

SMBG Information-Based Decision Support (PF, 2006-11): We have shown that automated behavioral feedback delivered in the field by a portable device can optimize glycemic control by reducing HbA1c and/or occurrence of severe hypoglycemia [33]. We tested the effect of an automated system providing real-time estimates of HbA1c, glucose variability, and risk for hypoglycemia. For 10 months, 120 adults with T1DM, performed SMBG and received feedback at three increasingly complex levels (3 months, each): (i) routine SMBG; (ii) estimated HbA1c, hypo risk, and glucose variability; (iii) estimates of symptoms potentially related to hypoglycemia. HbA1c, and hypoglycemia were evaluated at baseline and at the end of each level. This information-based decision-support reduced HbA1c from 8.0 to 7.6%, p=0.001 (effect confined to subjects with baseline HbA1c above 8.0. Incidence of symptomatic moderate/ severe hypoglycemia was reduced from 5.72 to 3.74 episodes/person per month (p=0.019), more prominently for subjects with history of SH or hypoglycemia unaware (*Figure 2*). We therefore concluded that feedback of SMBG data and summary SMBG-based measures can result in improvement in average glycemic control and reduction in moderate/severe hypoglycemia [33]. The system used in this study was an early prototype of the PF developed here but leveraging only SMBG data [33]. This technological limitation necessitated manual input of high measurement frequencies (4-10 SMBG per day). This investigation leverages automatically collected high frequency CGM data to further improve the usability of the PF system, as well as comparing the effect and acceptability of DSS to more prescriptive features.

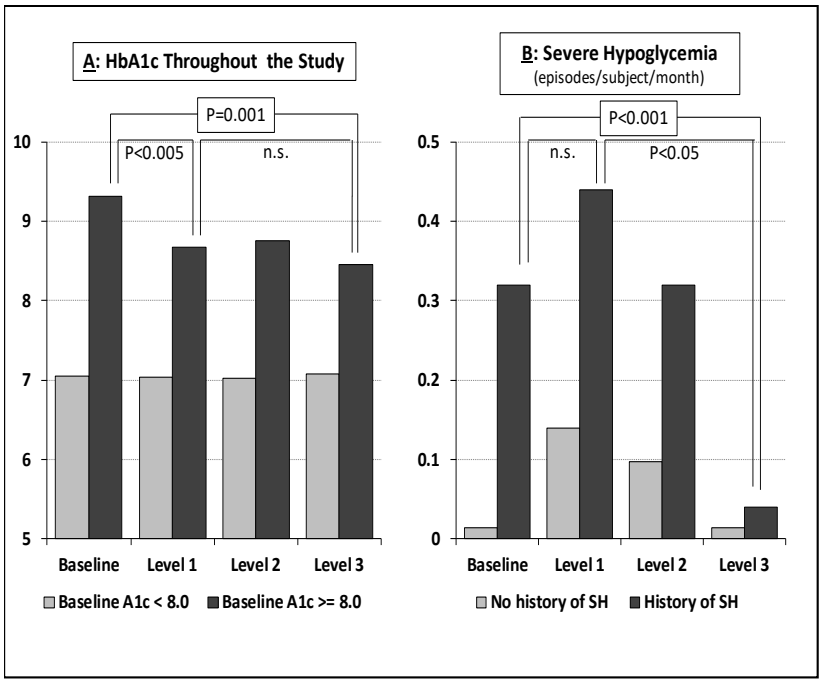

Figure 2: Results from 1-year automated decision-support intervention based on SMBG data, with 3 levels of feedback to the patient

Pilot study of Decision Support (DSS, 2012-2017): The feasibility and safety of a prototype DSS was tested in 15 women and 9 men with T1DM on insulin pump (N=16) or MDI (N=8),

NCT02558491. Age was 37±11 years old, average T1DM duration was 21±11 years. Participants were well controlled on average (HbA1c of 7.2±1%). Participants followed a non-blinded randomized crossover design, with two 48-hours observation periods where patients were exposed to a variety of meals and physical activities to challenge their own control strategies and the DSS. DSS was shown to be feasible and safe (no adverse events). Furthermore, GV was significantly improved (primary outcome, CGM coefficient of variation) from 0.36±0.08 during standard of care to 0.33±0.06 using DSS, p=0.045, with maximum effect during daytime. Further GV analysis using the Low and High blood glucose indices (LBGI, HBGI, [65]), confirmed that most of the observed improvement was due to the hypoglycemia-related GV measured by the LBGI: 2.5±2.1 to 1.6±1.3, p=0.042. As depicted in (Figure 3), protection from hypoglycemia was improved significantly while using the DSS: median percent time spent below 70mg/dL was reduced 3.5-fold, from 3.2% to 0.9%, p=0.018, while maintaining average glycemia 155±27mg/dL vs. 155±23mg/dL, p=0.86. [41]

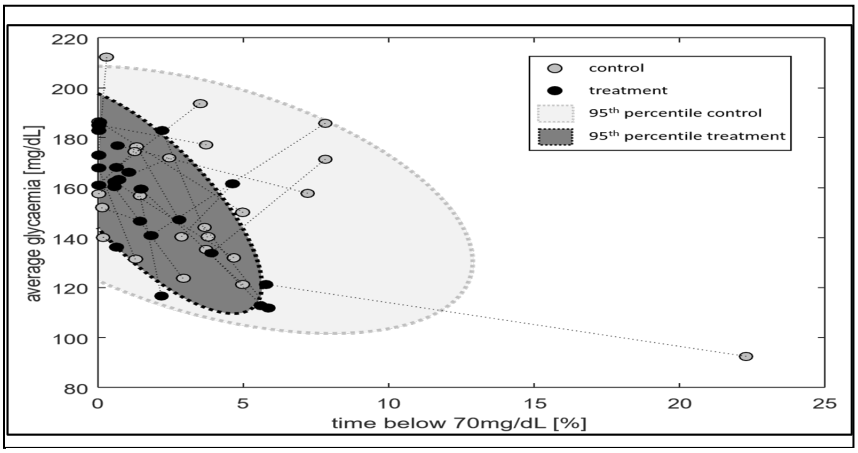

Figure 3: Impact of DSS on exposure to hypoglycemia and average glucose. Control (grey dots and envelop) and Treatment (black dot and dark grey envelop) are linked by the dotted line for each subject.

Ecological Momentary Analysis (EMA): Our research group has a long and prolific history in the use of EMA to study associations between glycemic parameters and psychosocial and behavioral variables. Our original EMA studies were conducted in the 1980s using pen and paper questionnaires completed just before SMBG, 3-5/day over several weeks. We investigated numerous aspects of living with T1D, including idiosyncratic symptoms associated with BG fluctuations [66-67], patient ability to recognize hypo- and hyperglycemia [68-69], adherence to SMBG recommendations, and relationships between BG extremes and mood state [70-71]. In the 1990s handheld personal computer technology replaced paper for the collection and storage of more complex daily diary data with date & time stamps. This technological advance allowed us to investigate relationships between diabetes self-management behaviors and BG patterns, as well as treatment decision-making (e.g. to drive or not when BG is low) [72-75].

As technology continued to advance, we were able to program daily diaries to include, not only questionnaires, but also brief cognitive tasks, which could be timed and scored. In a series of studies in the early 2000s [76-79], our group utilized PDAs to investigate cognitive performance in real-world settings at different BG levels in adults with T1DM and T2DM [77] and school-aged children [79]. Additionally, we conducted studies exploring the relationships between glycemic fluctuations and symptoms/moods in patients with T2DM [76] and the ability of young children and their parents to recognize hypoglycemia [78]. Leading to our first DSS system.

Over the past few years, our group has combined EMA approaches with CGM data collection in innovative ways to address clinically important questions regarding relationships between BG levels and behavioral variables, such as the association between psychological stress and BG patterns using CLC algorithms [80]; where we found a small but significant association between stress and glycemic instability. In 2017, we used the EMA approach in a study of the accuracy of Diabetes Alert Dogs, comparing daily diaries of dog alerts to blinded CGM data [81-82]. That study documented that accuracy at detecting hypoglycemia was highly variable across individual dogs and highlighted the need for standardized training and performance. Most recently, our team has completed a clinical trial using EMAs in a sample of older adults (age > 65) and children with T1DM to assess the cognitive impact of CLC; the data collection process was a success, but the analysis is still undergoing, and we expect to publish these results by the end of 2020. In addition to the above studies, our group also has a long history of using EMA approaches to collect pre- and post-intervention data in clinical trials of behavioral interventions [66-69], as proposed here. Taken together, there is ample evidence of our group's experience and expertise with research using EMA methods.

Based on these pilot results, we propose to move forward with demonstrating the superior efficacy of a CGM-based advisory system in T1DM, as compared to SAM, and with characterizing the impact of psycho-behavioral factors on system performance, which will enable system individualization and lead to automated adaptation of advice delivery to optimize glycemic control and reduce the system's psychological impact.

1.2. Specific Aims

Aim 1 (Control of Glucose Variability) We will confirm and contrast the efficacy of two previously designed technological interventions – Personalized Feedback (PF) and Decision Support System (DSS) - in reducing GV in T1DM during a 6-month randomized crossover clinical trial. This will allow us to show:

Aim 1.1 the superiority of the PF over Sensor-augmented mode (SAM) in controlling GV. PF is a system designed to provide patients with *actionable information* about glucose control in general and GV in particular (e.g. estimated HbA1c (eA1c), risk of hypoglycemia, and activity level);

Aim 1.2 the superiority of the DSS over SAM in controlling GV. DSS is a CGM-based system that includes PF and further assists with treatment recommendations for common metabolic challenges;

Aim 1.3 the overall non-inferiority of DSS over PF intervention to control GV and superiority of DSS to maintain tight glycemic control over time (lower variations of GV in time).

Aim 2 (personalization of treatment policy) We hypothesize that the participants in this study will have technology intervention preferences (e.g. PF or DSS) that can be predicted by key psychosocial and behavioral parameters and are prognostic of the level of GV control achievable by the intervention. We will:

Aim 2.1 confirm that technology acceptance and trust are predictive of the level of GV control achieved during the study (see Aim 1), regardless of the type of DSS system in use. We hypothesize that technology acceptance will correlate negatively with GV: i.e. higher technology acceptance leads to lower GV;

Aim 2.2 explore the impact of technology expectations and experience on the performance of each type of technology intervention (SAM, PF, DSS). For example, higher expectation will negatively correlate with GV for the SAM treatment, but not the DSS treatment.

Aim 2.3 assess the correlation between relevant psycho-behavioral traits with the performance of PF vs DSS, identifying potential pathways to the corresponding optimal technology-based treatment policies.

1.3. Outcomes

1.3.1. Glycemic outcomes

The primary outcome of this study will be Glucose Variability (GV) as measured by CGM-based Coefficient of Variation (CV), as recommended by the International Consensus on Use of Continuous Glucose Monitoring. To further characterize glucose control, we will compute other CGM Consensus outcomes as well:

Average

Percent in different ranges:

- <50 mg/dL
- <54 mg/dL

- <60 mg/dL
- <70 mg/dL
- ≤70-≤180 mg/dL
- >180 mg/dL
- >250 mg/dL
- >300 mg/dL

Each modality of treatment will be assessed using the last 4 weeks of CGM recordings, as we expect most of the GV benefits of each intervention to be realized within the first 4 weeks of the intervention, and a minimum of 24 days of data is considered optimal for CGM–based CV determination.

1.3.2. Glucose Variability Reduction Achieved with CGM-based expert systems

General linear models (GLM) (repeated measures ANOVA) will be used to assess the significance of the differences in average response between SAM, PF, and DSS across appropriate CGM-based metrics. The particular design of the clinical study allow for Aims 1.1, 1.2, and 1.3 to each be addressed independently in a randomized crossover analysis, as shown in Figure 4. While the randomized order of the interventions (escalation vs de-escalation) allows for an objective assessment of the average efficacy of each of them, we will introduce the order as a fixed factor to verify if significant study effects can be detected. Finally, we will study the evolution of GV within each modality period: GV and other CGM-based outcomes will be computed bi-weekly (the minimum length of time for precise GV assessment) and entered in a repeated measures GLM analysis; within-subject contrast (linear and polynomial) using 5 repeated measures per condition to explore the evolution of the glycemic outcomes in time; Aim 1.3.

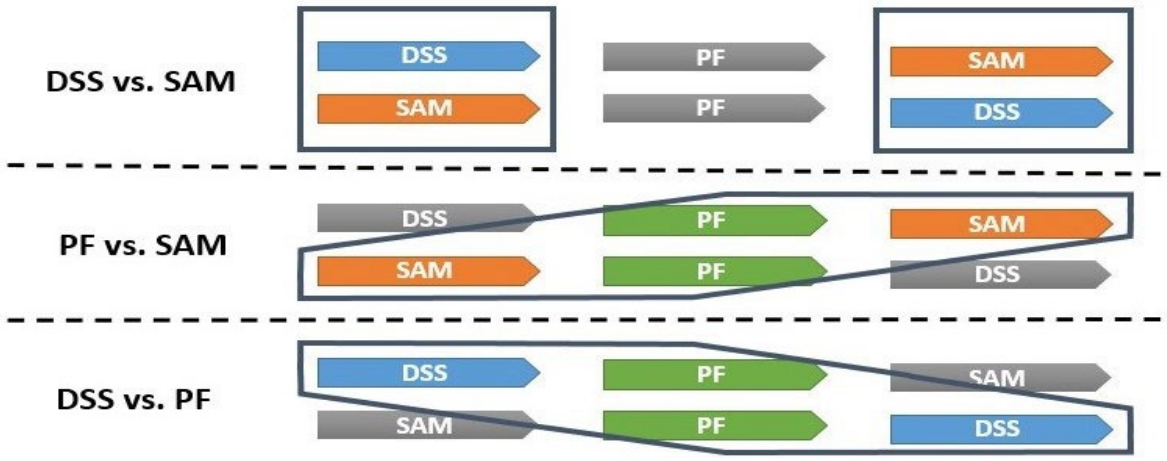

Figure 4: Multiple analyses enabled by study design to address Aim 1.1, 1.2 and 1.3

1.3.3. Exploration of the effect of treatment escalation vs. de-escalation

A key advantage of the proposed study design (beyond the optimal statistical power) is the possibility to explore the glucose control and psycho-behavioral impact of features being added and/or enhanced with prescriptive components (DSS), vs. features being limited to information (PF) or even removed (SAM). We will perform this analysis by looking at the between factors in the repeated ANOVA analysis, contrasting the escalation group vs. de-escalation group. While not powered, this analysis will provide key insights in the future feature adaptation schemes based on the ATI.

1.3.4. Psychological and Behavioral Questionnaires

As part of Aim 2, we will conduct robust psychosocial analyses of factors important to participant experience. This will examine relevant core constructs of trust, acceptance, satisfaction, confidence as well as fear, worries, distress and burden. Validated and reliable measures will be used to explore psycho-behavioral characteristics and outcomes in addition to specifically adapted measures for SAM and DSS technologies to capture holistic, disease-specific and technology-specific data. These questionnaires will evaluate how specific constructs are predictive of successful glycemic outcomes associated with DSS. These questionnaires will enable us to assess important non-glycemic treatment outcomes that are meaningful to patients including those affecting Quality of Life (QOL) (e.g. fear of hypoglycemia and diabetes distress). To those ends, participants will complete a battery of questionnaires related to diabetes management, treatment satisfaction and QOL at baseline (before system use) and after each treatment modality.

1.3.5. Ecological Momentary Assessment Data Collection

Participants will be trained on the EMA surveys and requirements. During each treatment condition, over the course of 2-3 days every two weeks, the participant will be asked to complete a “Daily Diary” with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase. The DiAs phone will display a text message containing a link to the survey. Surveys will be triggered at fixed times, including a morning survey ~1h after waking up and an end-of-the-day survey around 8-9 PM. Participants will be able to delay (up to 30 min) or skip (up to 2 per day excluding at wake up) surveys for their convenience. Participants will respond to questions on a 5-point Likert scale (0=Not at All, 4=Extremely). The first Diary for each day will contain two additional items for rating sleep quantity/quality. The Daily Diary questions are intended to assess agreement, trust, treatment satisfaction, diabetes burden, self-efficacy, mood valence, energy level, physical well-being, and concerns about hypo- and hyperglycemia. The first Diary for each day will contain two additional items for rating sleep quantity/quality.

1.3.6. Mapping of Psycho-behavioral Characteristics to DSS Preferences and Performance

Baseline assessments of psycho-behavioral traits will be introduced as covariates in the general linear model when analyzing the glycemic performance of each treatment modality (SAM, PF, DSS). Contrasts will be used to study each pair, specifically SAM vs any advisory system. For constructs that can be changed by the intervention itself (e.g. Fear of hypoglycemia) and that are therefore measured after each intervention, we will use repeated measures model with within-subject covariates (MIXED models) to understand their impact on DSS efficacy. This analysis will shed light on the relationship between the efficacy of treatment modality and individual patient characteristics; **Aims 2.1 and 2.2**

Using the cloud data system, we will isolate patient-system interactions for each advisory module (e.g. eA1c, predictive hypoglycemia alert), and compute for each subject the probability of the interaction to lead to the expected action, and positive glycemic outcomes. These probabilities will then be used as outcome variables in separate analysis to assess whether psycho-behavioral traits are associated with the acceptance of specific advisory functionalities (e.g. Fear of Hypoglycemia could be lowered by the hypoglycemia prediction module); answering **Aim 2.3.**

1.3.7. Identification and Validation of the Acceptance & Trust Index

Finally, we will use the validated trust and acceptance measures obtained throughout the protocol to validate the dynamic tracking of ATI. The 80 studied subjects will be divided in 4 cohorts of 20, the first 3 groups used to iteratively refine our estimation procedure (interaction quantification and dynamical model parameters) to accurately reproduce acceptance and trust fluctuations. The last group will be used to prospectively demonstrate the correlation between ATI, trust, and acceptance, thereby addressing **Aim 3.2**; retrospectively we will use the finalized method on all 80 participants to compute the auto-correlation between trust and acceptance and ATI and study the ability of ATI to track changes in time; **Aim 3.3**. Such an index, shown to follow the evolution of robustly assessed trust and acceptance (via standard methods) will enable future systems to characterize its interactions with its user, detecting early drop in adherence and disconnect with patient's expectation (fault detection), and potentially associating them with specific functionalities (fault classification), leading to self-adaptations capable of optimizing system use and trust.

1.4. Study Design

This is a randomized crossover study in T1DM designed to demonstrate the efficacy of personalized feedback (PF) and decision support (DSS) over sensor-augmented mode (SAM) therapy and to establish relationships between the level of glucose variability (GV) control achievable by the intervention and individual psycho-behavioral characteristics.

We plan to split the study into 4 cohorts of about 25 participants each (expected retention 20 per cohort). Each cohort will continue for ~7 months and will have the structure presented in Figure 5. Following recruitment, screening, and a run-in period of SAM, participants will be randomized into one of two groups: escalation vs. de-escalation of devices and function. Each treatment modality (SAM, PF, DSS) will continue for about 8 weeks, with the last 4 weeks used to assess GV from CGM data.

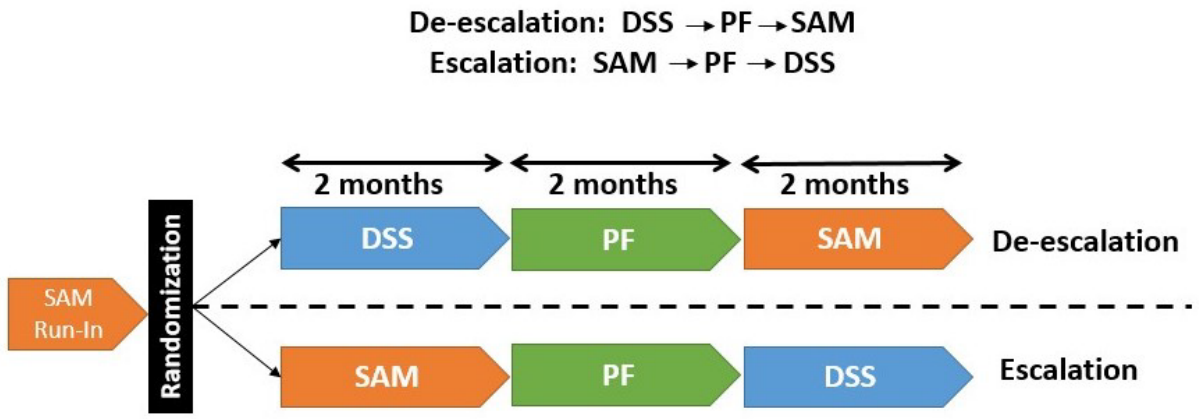

Figure 5: Study design and timeline

1.5. Study Participants

We anticipate recruiting a total of 100 adults aged 18 years and older. An equal numbers of males and females will attempt to be recruited and all racial/ethnic groups will be eligible for participation. Based on our experience in previous studies of this magnitude, we expect that 80% of recruited subjects will complete the entire trial. Enrollment in the study will proceed with the goal of completing approximately 80 subjects. Up to 150 participants may sign the consent form. Eligibility criteria ensure that the subject will be able to fully deploy the technology in this study. Exclusions include any known medical condition that in the judgment of the investigator might interfere with the completion of the protocol.

1.6. Clinical Sites

The study will be performed at the University of Virginia.

Chapter 2 Study Devices

2.1. Diabetes Assistant (DiAs)

The Diabetes Assistant (DiAs) system which is a medical platform that uses a smart-phone to connect to a continuous glucose sensor to insulin pump and run closed-loop control.

2.2. Insulin Pump

For CSII participants, the study system will include a modified Tandem t:slim X2 insulin pump (Tandem Diabetes Care, Inc., San Diego, CA), capable of communicating wirelessly with DiAs (t:AP).

2.3. Continuous Glucose Monitor (CGM)

The study CGM will include Dexcom G6® transmitter and sensors (Dexcom, Inc., San Diego, CA) connected to the Diabetes Assistant (DiAs).

2.4. Ketone Meter and Strips

Blood ketone levels will be measured using Precision Xtra® meters and strips (Abbott Laboratories Inc., Alemeda, CA) in accordance with the manufacturer's labeling. The blood glucose meter component of the Precision Xtra® will not be used.

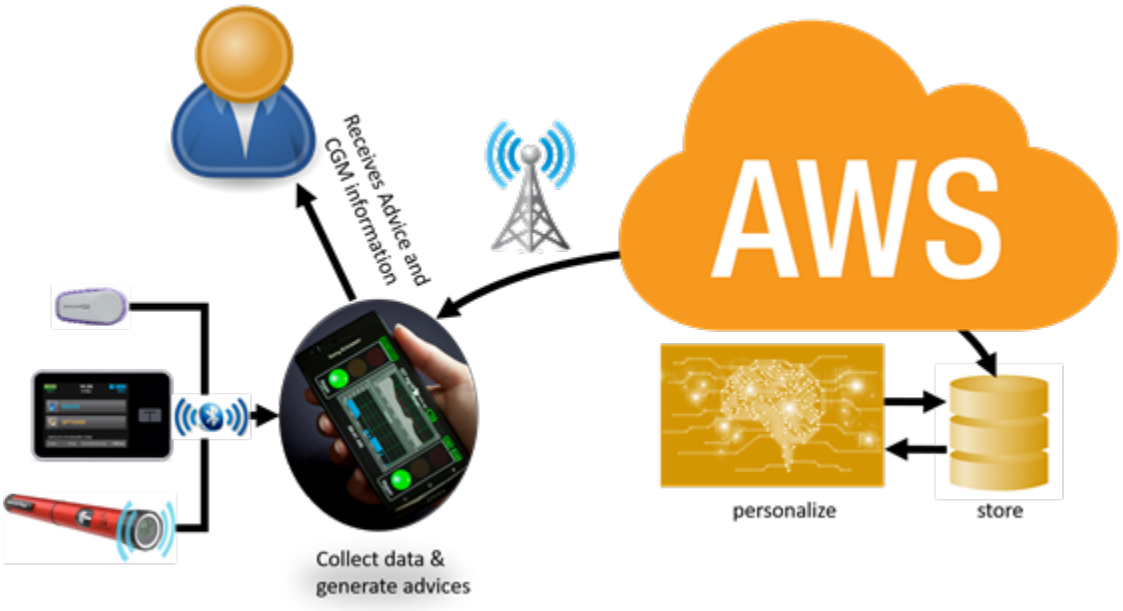

Figure 6: Study Equipment

Chapter 3 Study Screening

3.1. Informed Consent and Authorization Procedures

Before consent has been obtained, participants will be asked inclusion/exclusion criteria questions during prescreening to determine study eligibility. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. Potential eligibility may be assessed as part of a routine-care examination.

A participant is considered enrolled when the informed consent form has been signed by the participant and the study team.

Consenting procedures and documentation is defined in section 16.3.

Virtual study visits may take the place of all in-person study visits as deemed feasible by the study team.

3.2. Visit 1 - Eligibility Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed study personnel, blood draw and urine pregnancy testing (if applicable) to screen for exclusionary medical conditions.

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

- Inclusion and exclusion criteria assessed
- Demographics (address, date of birth, gender, race, ethnicity)
- Contact information
- Diabetic history
- Medical history
- Medications
- Physical examination (may use a medical record within the past 6 months)
- Weight, height (participant may self-report this information)
- Vital signs including measurement of blood pressure and pulse (may use a medical record within the past 6 months)
- Urine or serum pregnancy test for all females of child-bearing potential
- Chemistry panel, liver function tests, and thyroid stimulating hormone

- Diabetes Management Information: participant's typical insulin dosing routine including average total daily insulin use (calculated over 1 week), basal rates, carbohydrate ratio(s), and correction factor(s)

Screening procedures will last approximately 2 hours. Once all results of the screening evaluations are available, a decision will be made to determine the participant's eligibility for the study or if one or more part of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the participant will be excluded from participation with follow up and referred to their primary care physician as needed. The study physician may elect to rescreen participants and collect additional laboratory values if their clinical situation changes.

3.3. Participant Inclusion Criteria

The participants must meet all of the following inclusion criteria in order to be eligible to participate in the study.

- Age 18 years and older
- Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least one year
- HbA1c 6.0-11.0%, inclusive
- Demonstration of proper mental status and cognition for the study
- If on a non-insulin hyperglycemic therapy, stability on that therapy for the prior 3 months and willingness not to alter the therapy for the study duration.
- For females, not currently known to be pregnant
- If female and sexually active, must agree to use a highly effective form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study. Also, subjects who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
- Subjects must have Internet access and a computer system that meets the requirements for uploading the study equipment and ability to participate in video conferencing.
- Investigator has confidence that the subject can successfully operate all study devices and is capable of adhering to the protocol

3.4. Participant Exclusion Criteria

The participant must not have any exclusion criteria in order to be eligible to participate in the study.

- NPH (neutral protamine hagedorn) insulin
- Use of any medication that at the discretion of the investigator is deemed to interfere with the trial.
- Current treatment of a primary seizure disorder
- Coronary artery disease or heart failure, unless written clearance is received from a cardiologist.
- Hemophilia or any other bleeding disorder
- A known medical condition, which in the opinion of the investigator or designee, would put the participant or study at risk such as the following examples:
    - Inpatient psychiatric treatment in the past 6 months
    - Presence of a known adrenal disorder
    - Abnormal liver function test results (Transaminase >3 times the upper limit of normal)
    - Abnormal renal function test results (calculated GFR <60 mL/min/1.73m2).
    - Active gastroparesis requiring medical therapy
    - Uncontrolled thyroid disease (TSH undetectable or >10 mIU/L).
    - Abuse of alcohol or recreational drugs
    - Infectious process not anticipated to be resolved prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis, deep tissue infection).
    - Uncontrolled arterial hypertension (Resting diastolic blood pressure >100 mmHg and/or systolic blood pressure >180 mmHg).
    - Uncontrolled microvascular complications such as current active proliferative diabetic retinopathy defined as proliferative retinopathy requiring treatment (e.g. laser therapy or VEGF inhibitor injections) in the past 12 months.
- A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the protocol.
- Not familiar with smart phone technology
- Current use of the following drugs and supplements:

- Oral steroids
- Any other medication that the investigator believes is a contraindication to the subject's participation

- Participation in another pharmaceutical or device trial at the time of enrollment or during the study.

Screening procedures will last approximately 2 hours. Once all results of the screening evaluations are available, a decision will be made to determine the participant's eligibility for the study or if one or more parts of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the participant will be excluded from participation with follow up and referred to their primary care physician as needed. The study physician may elect to rescreen participants and collect additional laboratory values if their clinical situation changes.

3.5. Post-screening assessments

If the subject is deemed eligible to participate in the study, the subject will elect to use either continuous subcutaneous insulin infusion (CSII) or MDI therapy for the duration of the study, no changes are allowed during the study. Furthermore, the participant will elect to use carbohydrates counting or not for the computation of the meal bolus, this choice will apply to the entire study.

Participants will then go through a baseline psycho-behavioral assessment. The following questionnaires will be completed:

- Diabetes Specific Personality Questionnaire
- ABACUS
- Diabetes Locus of Control
- Confidence in Diabetes Self-Care Scale
- Clarke's Hypoglycemia Awareness Scale Participant Inclusion Criteria
- Demographic Data Survey (screening visit only)

Chapter 4 Training Visit

Participants may use CSII or multiple daily insulin (MDI) injection therapy for their diabetes management. Participants will be asked to maintain this treatment throughout the study. In the event that MDI participants elects to change to CSII therapy (see section 3.5), the run-in period will include a period of insulin stabilization for up to 6 weeks. The study physician may elect to extend this time frame if additional time would be beneficial to the participant.

If participants intend on identifying carbohydrate counting (carbohydrate ratio, insulin sensitivity factor and glucose goal) at mealtime, they will be asked to continue to provide this information throughout the study.

4.1. Visit 2 - Study Equipment

4.1.1. Study Continuous Glucose Monitor Training

A Dexcom G6 CGM will be provided to all participants at the training session. The participants will be provided with CGM equipment and instructed to use the study CGM on a daily basis. If the participant has prior use of the CGM, re-training will be specific to the individual. The study team may elect to have less frequent CGM users watch the Dexcom online training videos (https://www.dexcom.com/training-videos) to assist in the training session. Study staff training may include review of study CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Study staff will specifically identify how alarms are set using the app and the frequency that these alarms will repeat when enabled.

The participants personal CGM will be discontinued. The participants will be observed placing the sensor and will learn/review how to access the CGM trace. The participants will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labeling of the study CGM device.

An electronic copy of the CGM user's guide will be provided for the participants to take home. The study team will be sure that the participants will leave the clinic knowing how to properly use the CGM.

Upon request, the study team will provide a Dexcom receiver to allow participants to share their CGM data with their personal care providers.

4.1.2. Study Pump (Tandem t:AP) Training (CSII participants)

Eligible participants will be fully instructed on the study insulin pump. A qualified staff member will conduct the training and discuss particular differences from the home pump in important aspects such as calculation of insulin on board and correction boluses.

Additional training topics are not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.

The study pump will be programmed with the subject's usual basal rates and pump parameters.

The study team will assist the subject in study pump infusion site initiation and will assist the subject on starting the study pump.

The subject's personal pump will be removed.

The subject will be supervised with the study pump during at least one meal or snack bolus to ensure subject understanding of the pump features.

The subject will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.

4.1.3. DiAs Training

Prior to initial use, the DiAs will be initialized by a study team member with the participant's individual insulin dosing parameters, including carbohydrate ratio, insulin sensitivity factor and basal insulin doses. If applicable, the study team will confirm the carbohydrate counting parameters entered in the system with the study physician.

Qualified study team members will train the subject in performing specific tasks including the following:

- How to view the CGM information including the most recent CGM value, trend arrow, and CGM graph. Low and high threshold alerts will be set. The patient may choose the threshold alert values, but the low alert may not be set to <70 mg/dL and the high alert may not exceed 300 mg/dL.
- How to connect the CGM transmitter to DiAs as well as troubleshooting techniques for reconnecting. If the CGM values are not available, the subject will be asked to perform fingerstick BG measurements for insulin dosing and treatment management.
- How to start and stop a sensor session with the DiAs APP.
- [for CSII participants] How to connect the pump to DiAs and troubleshooting steps for reconnection.
- [For MDI participants] How to retroactively inform the system of past insulin doses
- How to activate the "meal" screen of the DiAs system any time meal insulin or additional correction insulin is desired. And how to use the selected bolus calculator (different if counting carbohydrates or not, see section 3.5).

- How to inform the system of hypoglycemia treatment via a “hypoglycemia treatment” button on the DiAs user interface after glucose is consumed that is not accompanied by an insulin bolus.
- What to do when exercising while using the system and how to use a temporary basal rate.
- How to accept DiAs mode changes sent remotely by the study team.

DiAs instructions will be provided in the study training manual.

4.1.4. Ketone Meter Training

Subjects will be provided with a study blood ketone meter, test strips, and standard control solution to perform QC testing per manufacturer guidelines. QC will be completed prior to subject receiving the study ketone meter. Only meters that read within the target range at two concentrations per manufacturer labeling will be used in the study. The subject will be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.

Subjects will be instructed to perform blood ketone testing per the Glycemic Treatment Guidelines located in the study training manual.

4.2. Ecological Momentary Assessment Training

After randomization, all participants will be trained on how to access and complete EMAs from their study phone, how to postpone alerts, and enter a voluntary diary. Participants will be informed when the EMAs are scheduled during each phase of the trial.

4.3. Glucagon Emergency Kit

A home glucagon emergency kit will be required. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

Chapter 5 Study Procedures

5.1. Study Contacts

5.1.1. Study Support

Participants will also receive study staff contact information to ask any questions they may have during the study. Additionally, participants will be provided with study contact information for technical support with DiAs System, the study insulin pump and the study CGM. The participant will be asked to call the study team at any time during the study for any health-related issues (adverse events), including hypoglycemia <54 mg/dL, frequent highs >300 mg/dL, or ketones ≥3.0 mmol/L. The participant may use the study pump and study CGM during periods of DiAs disconnections or technical difficulties.

5.1.2. Web Conferencing

Study visits may be completed using HIPAA compliant web conference tool. The study team will provide the participant with the meeting information in advance of the appointment.

5.2. Sensor-Augmented Mode (SAM) Run-in Period

5.2.1. CGM use

Once all training activities are completed, the participant will be given adequate supplies to complete the Run-in home use of the DiAs system in SAM.

Participants will complete a minimum of 14 days (if CGM use within the preceding 3 months) or 4 weeks (if no CGM use within the preceding 3 months) of home use of the DiAs system in SAM. The study physician may request an additional run-in period of 2 weeks.

The participant will be informed that in order to be eligible for the study, the DiAs system in SAM must be used on a minimum of 11 out of 14 days for CGM users or 22 out of 28 days CGM nonusers.

An appointment for Visit 3 will be scheduled.

5.2.2. Questionnaires

Participants will be sent the following questionnaires on the final week of the Run-in Period and will be asked to complete them within 1 week:

- T1-Diabetes Distress Scale
- Hypoglycemia Fear Survey

- Hyperglycemia Avoidance Scale

5.3. Visit 3 – Eligibility Assessment, Randomization and Training

The participant may complete this visit via web conferencing and/or at the study site.

5.3.1. Eligibility Assessment

The CGM and insulin data will be reviewed to assess whether the subject has used the DiAs system in SAM on at least 11 out of 14 days for CGM users or 22 out of 28 days for non-CGM users. Subjects who are unable to meet the CGM and DiAs compliance requirement will be withdrawn from the study, unless the investigator believes that there were extenuating circumstances that prevented successful completion. In such cases, the investigator may ask the participant to repeat this eligibility assessment.

5.3.2. Adverse Event Assessment

The participant will be asked about any of adverse events, adverse device effects, and device issues since the last visit. The participant will also be asked if there were any low BGs <54 mg/dL, high BGs >300 mg/dL, or ketones ≥3.0 mmol/L since the last visit. Participants will be encouraged to contact the study team between visits as needed (i.e. report adverse events in real-time).

Chapter 6 Study Procedures - Escalation

6.1.1. Randomization to Escalation

Eligible subjects will be randomized to therapy escalation (SAM→PF→DSS).

A baseline Hemoglobin A1C will be collected. The participant will receive a mode change for Phase 1 according to the randomization scheme.

6.2. Sensor Augmented Mode

Participants randomized to escalation will have any questions answered about continuing use of the DiAs system in SAM.

6.2.1. SAM EMA Surveys

Over the course of 2-3 days every two weeks of Phase 2, the participant will be asked to complete a "Daily Diary" with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

6.2.2. Phase 1 Initiation Questionnaires

Participants randomized to escalation will complete the following questionnaires:

- Pittsburgh Sleep Quality Index

Once all training activities are completed, the participant will be given adequate supplies and study devices to last until the subsequent clinic visit. An appointment for Visit 4 will be scheduled

6.3. Home Use of DiAs in Phase 1 Mode

The participant will complete a minimum of 8 weeks of DiAs use in Phase 1 Mode at home. During the course of Phase 1, participants will complete EMA surveys and post-phase questionnaires.

6.3.1. Phase 1 EMA Surveys

Over the course of 2-3 days every two weeks of Phase 1, the participant will be asked to complete a "Daily Diary" with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

6.3.2. Post-Phase 1 Questionnaires Week 7

Participants randomized to escalation will be sent the following questionnaires on week 7 (day 42 of Phase 1) and will be asked to complete them within 1 week:

- Pittsburgh Sleep Quality Index

- Hyperglycemia Avoidance Scale

6.3.3. Post-Phase 1 Questionnaires Week 8

Participants randomized to escalation will sent the following questionnaires on week 8 (day 49 of Phase 1) and will be asked to complete them within 1 week:

- Confidence in Diabetes Self-Care Scale
- T1-Diabetes Distress Scale
- Hypoglycemia Fear Survey

6.4. Visit 4 – Phase 2 Initiation

All participants in each randomization scheme use PF in Phase 2. Phase 2 initiation may be conducted either via web conference or an office visit. The participant will remotely receive a mode change for Phase 2. Study staff will review the features of the Personalized Feedback (PF) mode and answer any questions. Participant will have a blood/urine pregnancy test that must be negative in order to continue to participate in this study.

6.4.1. Training on Phase 2 DiAs Mode

The participant will be trained on the following features of the Personalized Feedback System:

- **Tracking of estimated HbA1c:** When properly calibrated, eA1c is within 0.3% of reference HbA1c on average, and within 1% of HbA1c >95% of the time.
- **Hypoglycemia Risk Indicator:** Provides an indication of the current risk for hypoglycemia.
- **Insulin Sensitivity Profile & Indicator:** Tracks changes in insulin sensitivity (SI) and creates daily and monthly SI profiles.
- **Insulin on Board:** Tracks active insulin to avoid insulin stacking using a common 4-6 hour action curve.
- **Personalized weekly feedback.** Provides advice to the user on what went well in terms of glycemic control and system use in the past week and what may be a good thing to focus on for the following week.

6.4.2. Phase 2 Initiation Questionnaires

Participants randomized to escalation will complete the following questionnaires:

- Technology Expectations (burdens subscale only)
- INSPIRE (revised for DSS)

6.4.3. Adverse Event Assessment

The participant will be asked about any of adverse events, adverse device effects, and device issues since the last visit. The participant will also be asked if there were any low BGs <54 mg/dL, high BGs >300 mg/dL, or ketones ≥3.0 mmol/L since the last visit.

Once all training activities are completed, the participant will be given adequate supplies and study devices to last until the subsequent clinic visit. An appointment for Visit 5 will be scheduled. Participants will be encouraged to contact the study team between visits as needed (i.e. report adverse events in real-time).

6.5. Home Use of DiAs in Phase 2 Mode

The participant will complete a minimum of 8 weeks of DiAs use in Phase 2 Mode at home.

During the course of Phase 2, participants will complete EMA surveys and post-phase questionnaires.

6.5.1. Phase 2 EMA Surveys

Over the course of 2-3 days every two weeks of Phase 2, the participant will be asked to complete a "Daily Diary" with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

6.5.2. Post-Phase 2 Questionnaires Week 7

All participants will be sent the following questionnaires on week 7 (day 42 of Phase 2) and will be asked to complete them within 1 week:

- Technology Acceptance (burdens subscale only)
- Pittsburgh Sleep Quality Index
- T1-Diabetes Distress Scale

6.5.3. Post-Phase 2 Questionnaires Week 8

All participants will be sent the following questionnaires on week 8 (day 49 of Phase 2) and will be asked to complete them within 1 week:

- Hypoglycemia Fear Survey
- Hyperglycemia Avoidance Scale
- Confidence in Diabetes Self-Care Scale

6.6. Visit 5 – Phase 3 Initiation

The participant will begin Phase 3 according to the randomization scheme either via web conference or an office visit. The participant will remotely receive a mode change for Phase 3. Study staff will review the features of the Phase 3 system and answer any questions. Participant will have a blood/urine pregnancy test that must be negative in order to continue to participate in this study.

6.6.1. Training on Phase 3 DiAs Mode

Participants randomized to escalation will be trained to use DiAs in DSS mode, including the following features:

- **Exercise Advice:** An advisory module that ensures safety of mild to moderate exercise by predicting whether an exercise bout is likely to result in hypoglycemia and providing a graded carbohydrate supplementation strategy and possible reduction in insulin advice.
- **Bedtime Advice:** Gauges overnight hypoglycemia risk and provides bedtime carbohydrate advice.
- **Smart Bolus Calculator:** An advanced bolus calculator capable of accounting for several factors such as exercise (activity on board), metabolic characteristics (correction based on 45 min predicted glucose to account for insulin delays) and SI fluctuations (insulin sensitivity tracker).
- **Treatment Parameter Optimization:** An optimization routine that analyzes the previous 30 days of CGM, insulin, and meal data to provide updated insulin treatment parameters (CR, CF, and basal rate) to minimize glycemic risk.

6.6.2. Phase 3 Initiation Questionnaires

Participants randomized to escalation will complete the following questionnaires:

- Technology Expectations (burdens subscale only)
- INSPIRE (revised for DSS)
- Diabetes Locus of Control

6.6.3. Adverse Event Assessment

The participant will be asked about any of adverse events, adverse device effects, and device issues since the last visit. The participant will also be asked if there were any low BGs <54 mg/dL, high BGs >300 mg/dL, or ketones ≥3.0 mmol/L since the last visit. Participants will be encouraged to contact the study team between visits as needed (i.e. report adverse events in real-time).

6.7. Home Use of DiAs in Phase 3 Mode

The participant will complete a minimum of 8 weeks of Phase 3 at home. During the course of Phase 3, participants will complete EMA surveys and post-phase questionnaires.

6.7.1. Phase 3 EMA Surveys

Over the course of 2-3 days every two weeks of Phase 3, the participant will be asked to complete a "Daily Diary" with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

6.7.2. Post-Phase 3 Questionnaires Week 7

Participants randomized to escalation will be sent the following questionnaires on week 7 (day 42 of Phase 1) and will be asked to complete them within 1 week:

- Technology Acceptance (burdens subscale only)
- Pittsburgh Sleep Quality Index.
- T1-Diabetes Distress Scale

6.7.3. Post-Phase 3 Questionnaires Week 8

Participants randomized to escalation will sent the following questionnaires on week 8 (day 49 of Phase 3) and will be asked to complete them within 1 week:

- Hypoglycemia Fear Survey
- Hyperglycemia Avoidance Scale
- Confidence in Diabetes Self-Care Scale

6.8. Visit 6 - Study Exit

Participants will participate in a Study Exit visit either via web conference or an office visit. Participants will return to their standard diabetes care using their personal equipment. The study team will be available to answer questions about insulin parameters.

The participant will be asked to return all investigational study devices (e.g. study insulin pump, study, CGM, study phone, other associated supplies) either via mail or at an office visit. Participants may keep the study glucometer and ketone meter.

6.8.1. Study Exit Questionnaires

Participants randomized to escalation will complete the following questionnaires:

- ABACUS

- INSPIRE (revised for DSS)
- Diabetes Locus of Control

6.8.2. Adverse Event Assessment

The participant will be asked about any of adverse events, adverse device effects, and device issues since the last visit. The participant will also be asked if there were any low BGs <54 mg/dL, high BGs >300 mg/dL, or ketones ≥3.0 mmol/L since the last visit.

6.9. Post Study Check-In Visit (Visit 7)

Approximately 48 hours after the home use of the equipment, the study team will contact the participant via phone/email/text to assess:

- Adverse events, adverse device effects, and device issues
- Blood glucose values <60 mg/dL and >300 mg/dL

Chapter 7 Study Procedures – De-Escalation

7.1. Randomization to De-Escalation

Eligible subjects will be randomized to therapy de-escalation (DSS→PF→SAM).

A baseline Hemoglobin A1C will be collected.

The participant will receive a mode change for Phase 1 according to the randomization scheme.

7.2. Training on Phase 1 DiAs Mode

Participants randomized to de-escalation will be trained to use DiAs in DSS mode, including the following features:

- **Exercise Advice:** An advisory module that ensures safety of mild to moderate exercise by predicting whether an exercise bout is likely to result in hypoglycemia and providing a graded carbohydrate supplementation strategy and possible reduction in insulin advice.
- **Bedtime Advice:** Gauges overnight hypoglycemia risk and provides bedtime carbohydrate advice.
- **Smart Bolus Calculator:** An advanced bolus calculator capable of accounting for several factors such as exercise (activity on board), metabolic characteristics (correction based on 45 min predicted glucose to account for insulin delays) and SI fluctuations (insulin sensitivity tracker).
- **Treatment Parameter Optimization:** An optimization routine that analyzes the previous 30 days of CGM, insulin, and meal data to provide updated insulin treatment parameters (CR, CF, and basal rate) to minimize glycemic risk.

7.2.1. Phase 1 EMA Surveys

Over the course of 2-3 days every two weeks of Phase 2, the participant will be asked to complete a “Daily Diary” with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

7.2.2. Phase 1 Initiation Questionnaires

Participants randomized to de-escalation will complete the following questionnaires:

- Pittsburgh Sleep Quality Index
- Technology Expectations (burdens subscale only)
- INSPIRE (revised for DSS)

Once all training activities are completed, the participant will be given adequate supplies and study devices to last until the subsequent clinic visit. An appointment for Visit 4 will be scheduled.

7.3. Home Use of DiAs in Phase 1 Mode

The participant will complete a minimum of 8 weeks of DiAs use in Phase 1 Mode at home. During the course of Phase 1, participants will complete EMA surveys and post-phase questionnaires.

7.3.1. Phase 1 EMA Surveys

Over the course of 2-3 days every two weeks of Phase 1, the participant will be asked to complete a "Daily Diary" with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

7.3.2. Post-Phase 1 Questionnaires Week 7

Participants randomized to de-escalation will be sent the following questionnaires on week 7 (day 42 of Phase 1) and will be asked to complete them within 1 week:

- Technology Acceptance (burdens subscale only)
- Pittsburgh Sleep Quality Index
- T1-Diabetes Distress Scale

7.3.3. Post-Phase 1 Questionnaires Week 8

Participants randomized to de-escalation will be sent the following questionnaires on week 8 (day 49 of Phase 1) and will be asked to complete them within 1 week:

- Hypoglycemia Fear Survey
- Hyperglycemia Avoidance Scale
- Confidence in Diabetes Self-Care Scale

7.4. Visit 4 – Phase 2 Initiation

All participants in each randomization scheme use PF in Phase 2. Phase 2 initiation may be conducted either via web conference or an office visit. The participant will remotely receive a mode change for Phase 2. Study staff will review the features of the Personalized Feedback (PF) mode and answer any questions.

7.4.1. Training on Phase 2 DiAs Mode

The participant will be trained on the following features of the Personalized Feedback System:

- **Tracking of estimated HbA1c:** When properly calibrated, eA1c is within 0.3% of reference HbA1c on average, and within 1% of HbA1c >95% of the time.
- **Hypoglycemia Risk Indicator:** Provides an indication of the current risk for hypoglycemia.

- **Insulin Sensitivity Profile & Indicator:** Tracks changes in insulin sensitivity (SI) and creates daily and monthly SI profiles.
- **Insulin on Board:** Tracks active insulin to avoid insulin stacking using a common 4-6 hour action curve.
- **Personalized weekly feedback.** Provides advice to the user on what went well in terms of glycemic control and system use in the past week and what may be a good thing to focus on for the following week.

7.4.2. Phase 2 Initiation Questionnaires

Participants randomized to de-escalation will complete the following questionnaires:

- Technology Expectations (burdens subscale only)
- INSPIRE (revised for DSS)
- Diabetes Locus of Control

7.4.3. AE Assessment

The participant will be asked about any of adverse events, adverse device effects, and device issues since the last visit. The participant will also be asked if there were any low BGs <54 mg/dL, high BGs >300 mg/dL, or ketones ≥3.0 mmol/L since the last visit.

Once all training activities are completed, the participant will be given adequate supplies and study devices to last until the subsequent clinic visit. An appointment for Visit 5 will be scheduled.

7.5. Home Use of DiAs in Phase 2 Mode

The participant will complete a minimum of 8 weeks of DiAs use in Phase 2 Mode at home.

During the course of Phase 2, participants will complete EMA surveys and post-phase questionnaires.

7.5.1. Phase 2 EMA Surveys

Over the course of 2-3 days every two weeks of Phase 2, the participant will be asked to complete a “Daily Diary” with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

7.5.2. Post-Phase 2 Questionnaires Week 7

All participants will be sent the following questionnaires on week 7 (day 42 of Phase 2) and will be asked to complete them within 1 week:

- Technology Acceptance (burdens subscale only)

- Pittsburgh Sleep Quality Index
- T1-Diabetes Distress Scale

7.5.3. Post-Phase 2 Questionnaires Week 8

All participants will be sent the following questionnaires on week 8 (day 49 of Phase 2) and will be asked to complete them within 1 week:

- Hypoglycemia Fear Survey
- Hyperglycemia Avoidance Scale
- Confidence in Diabetes Self-Care Scale

7.6. Visit 5 – Phase 3 Initiation

The participant will begin Phase 3 according to the randomization scheme either via web conference or an office visit. The participant will remotely receive a mode change for Phase 3. Study staff will review the features of the Phase 3 system and answer any questions.

7.6.1. Training on Phase 3 DiAs Mode

Participants randomized to de-escalation will have any questions answered about resuming use of the DiAs system in SAM.

7.6.2. Phase 3 Initiation Questionnaires

Participants randomized to de-escalation will complete the following questionnaires:

- INSPIRE (revised for DSS)
- Diabetes Locus of Control

7.6.3. Adverse Event Assessment

The participant will be asked about any of adverse events, adverse device effects, and device issues since the last visit. The participant will also be asked if there were any low BGs <54 mg/dL, high BGs >300 mg/dL, or ketones ≥3.0 mmol/L since the last visit.

Once all training activities are completed, the participant will be given adequate supplies and study devices to last until the subsequent clinic visit. An appointment for Visit 6 will be scheduled. Participants will be encouraged to contact the study team between visits as needed (i.e. report adverse events in real-time).

7.7. Home Use of DiAs in Phase 3 Mode

The participant will complete a minimum of 8 weeks of Phase 3 at home. During the course of Phase 3, participants will complete EMA surveys and post-phase questionnaires.

7.7.1. Phase 3 EMA Surveys

Over the course of 2-3 days every two weeks of Phase 3, the participant will be asked to complete a "Daily Diary" with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

7.7.2. Post-Phase 3 Questionnaires Week 7

Participants randomized to de-escalation will be sent the following questionnaires on week 7 (day 42 of Phase 1) and will be asked to complete them within 1 week:

- Pittsburgh Sleep Quality Index
- T1-Diabetes Distress Scale

7.7.3. Post-Phase 3 Questionnaires Week 8

Participants randomized to de-escalation will be sent the following questionnaires on week 8 (day 49 of Phase 1) and will be asked to complete them within 1 week:

- Hypoglycemia Fear Survey
- Hyperglycemia Avoidance Scale (HAS)
- Confidence in Diabetes Self-Care Scale

7.8. Visit 6 - Study Exit

Participants will participate in a Study Exit visit either via web conference or an office visit. Participants will return to their standard diabetes care using their personal equipment. The study team will be available to answer questions about insulin parameters.

The participant will be asked to return all investigational study devices (e.g. study insulin pump, study, CGM, study phone, other associated supplies) either via mail or at an office visit. Participants may keep the study glucometer and ketone meter.

7.8.1. Study Exit Questionnaires

Participants randomized to de-escalation will complete the following questionnaires:

- ABACUS

7.8.2. Adverse Event Assessment

The participant will be asked about any of adverse events, adverse device effects, and device issues since the last visit. The participant will also be asked if there were any low BGs <54 mg/dL, high BGs >300 mg/dL, or ketones ≥3.0 mmol/L since the last visit.

7.9. Post Study Check-In Visit (Visit 7)

Approximately 48 hours after the home use of the equipment, the study team will contact the participant via phone/email/text to assess:

- Adverse events, adverse device effects, and device issues
- Blood glucose values <60 mg/dL and >300 mg/dL

Chapter 8 Testing Procedures

8.1. Laboratory / Point of Care Testing

8.1.1. HbA1c

- A blood sample will be obtained at screening to obtain a baseline hemoglobin A1c level.
- HbA1c level may be measured by study team using the DCA2000, a comparable point of care device, at time of screening
- Labs may be obtained at a local laboratory (e.g. LabCorp) convenient to the participant.
- Blood test may be obtained within 14 days prior to enrollment may be used for eligibility purposes.
- Sample collected at randomization and end of study will be used for statistical purposes.

8.1.2. Comprehensive Metabolic Panel

- A blood sample will be obtained at screening to assess kidney and liver functioning.
- Labs may be obtained at a local laboratory (e.g. LabCorp) convenient to the participant.
- Blood test may be obtained within 14 days prior to enrollment may be used for eligibility purposes.

8.1.3. Thyroid Stimulating Hormone

- A blood sample will be obtained at screening to assess thyroid function.
- Labs may be obtained at a local laboratory (e.g. LabCorp) convenient to the participant.
- Blood test may be obtained within 14 days prior to enrollment may be used for eligibility purposes.

8.1.4. Pregnancy Test

A blood/urine pregnancy test will be required for women of childbearing potential at the screening visit, and between each phase . Tests must be negative to participate in the study.

Chapter 9 Questionnaires & Ecological Momentary Analysis

9.1. Diabetes Specific Personality Questionnaire

The Diabetes Specific Personality Questionnaire is based on the original Six Factor Personality Questionnaire [81], a well-validated measure that was adapted for the diabetes-specific version of the questionnaire. The Six Factor Personality Questionnaire is a measure of six personality dimensions each consisting of three facet scales, measured by 108 Likert items. The Six Factor Personality Questionnaire facet scales are organized in terms of six factor scales. The Diabetes Specific Personality Questionnaire assesses three personality factors – conscientiousness, obsessive-compulsiveness, and openness. In this study, the Diabetes Specific Personality Questionnaire is used to explore whether personality type is associated with willingness and/or ability to effectively engage with the DSS. Administration time is approximately 15 minutes.

9.2. ABACUS

This is a structured interview used to provide a very brief assessment of carbohydrate counting and diabetes self-management skills important to effective engagement consisting of a series of 25 questions assessing health literacy and health numeracy in people with T1DM [84]**.**. The interviewer evaluates the subject answer to each question on a scale ranging from 1 (No competency) to 3 (Full competency); the sum yields to a total score. The higher the score, the higher the levels of health literacy and numeracy of the subject. Administration time is approximately 10-20 minutes.

9.3. Diabetes Locus of Control

This questionnaire [85] was developed for use on adults (18-80 y.o.) The scale consists of 18 items measuring the individual's personal beliefs about their control over their diabetes management and outcome: 6 items measuring internal locus of control, 6 items measuring powerful others locus of control, and 6 items measuring chance locus of control. A 6-point Likert-type scale is used in which 0 indicates 'strongly disagree with the statement' and 5 indicates 'strongly agree with the statement.' Administration time is approximately 5 minutes.

9.4. Confidence in Diabetes Self-Care Scale

This is a short 20-item self-report questionnaire assessing self-efficacy, the perceived ability to perform diabetes self-care tasks, in patients with T1DM [87]. Items are constructed to cover all domains of self-care as well as social skills. Each item is preceded by, "I believe I can…" with the strength of this belief rated on a 5-point Likert scale ranging from 1 ("No, I am sure I cannot") to 5 ("Yes, I am sure I can"). Administration time is approximately 10 minutes.

9.5. Clarke's Hypoglycemia Awareness Scale

The scale comprises eight questions characterizing the participant's level of hypoglycemia awareness, as well as risk for exposure to episodes of moderate and severe hypoglycemia [88]. It also examines the glycemic threshold for symptomatic responses to hypoglycemia. A score of four or more on a scale of 0 to 7 implies impaired awareness of hypoglycemia. Administration time is approximately 5 minutes.

9.6. The Diabetes Distress Scale

This is a measure that reflects diabetes-specific quality of life and emotional well-being [90]. The Diabetes Distress Scale is a measure of diabetes-related distress over a number of domains (e.g. diabetes management regimen, interpersonal distress) and consists of a scale of 17 items. These include items from each of four domains central to diabetes-related emotional distress. Patients rate the degree to which each item is currently problematic for them on a 6-point Likert scale, from 1 (no problem) to 6 (serious problem). Administration time is approximately 5 minutes.

9.7. Hypoglycemia Fear Survey

This questionnaire will be used to determine if the PF and DSS is associated with reduced fear of hypoglycemia. The Hypoglycemia Fear Survey-II [91] was developed to measure behaviors and worries related to fear of hypoglycemia in adults with T1DM. It is composed of 2 subscales, the Behavior and Worry. Behavior items describe behaviors in which patients may engage to avoid hypoglycemic episodes and/or their negative consequences (e.g., keeping blood glucose levels higher, making sure other people are around, and limiting exercise or physical activity). Worry items describe specific concerns that patients may have about their hypoglycemic episodes (e.g., being alone, episodes occurring during sleep, or having an accident). Items are rated on a 5-point Likert scale (0=never, 4=always), with higher scores indicating higher fear of hypoglycemia. Administration time is approximately 10 minutes.

9.8. Hyperglycemia Avoidance Scale

This measure is used to assess the extent of potentially problematic avoidant attitudes and behaviors in people with T1DM [91]. The Hypoglycemia Avoidance Scale reliably quantifies affective and behavioral aspects of hyperglycemia avoidance and is used to assess the extent of potentially problematic avoidant attitudes and behaviors regarding hyperglycemia in people with T1DM. It has 24 items plus two additional optional items asking about the highest level of daily blood glucose or HbA1c measures the individual would feel comfortable having. Administration time is approximately 10 minutes.

9.9. Pittsburgh Sleep Quality Index

This questionnaire will be used to assess whether the PF and DSS improve sleep quality and quantity. The Pittsburgh Sleep Quality Index [93] is a self-report questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, creating 7 components that produce one global score: the higher the global score, the poorer the sleep quality. Administration time is approximately 5-10 minutes.

9.10. Technology Acceptance and Expectations Survey (burdens subscale only)

The Technology Acceptance Surveys [94-95] were developed for an artificial pancreas camp study in adolescents. The 38 items in the questionnaire were based on interviews conducted with individuals who had participated in previous artificial pancreas trials about their experience regarding the device. It was subsequently adapted to assess these same measures for the PF and DSS. It assesses both positive and negative experiences with PF and DSS, including blood glucose management, device burden, and overall satisfaction. Items are rated on a 5-point scale. In this study only the burden subscale will be used. The Technology Expectations Survey has the same items included on the Technology Acceptance Survey but asks whether the individual expects to experience the various benefits and burdens from use of a device. Administration time is approximately 10 minutes.

9.11. INSPIRE (revised for DSS)

This questionnaire will be used to assess patient preferences to support effective onboarding and successful continued use of the PF and DSS. The INSPIRE survey was developed to assess various aspects of a user's experience regarding automated insulin delivery for both patients and family members. The surveys include various topics important to patients with T1DM and their family members based upon >200 hours of qualitative interviews and focus groups. It was adapted by its developer for use with the PF and DSS. The survey includes 22 items. Response options include a 5-point Likert scale from strongly agree to strongly disagree, along with an N/A option. Administration time is approximately 5 minutes.

9.12. Ecological Momentary Analysis (EMA)

In addition to the behavioral data automatically recorded (e.g. insulin dosing, interactions with system), an EMA procedure will be used to track the users' daily experiences of trust in the system, emotional well-being, treatment satisfaction, and diabetes-related concerns and burden. Using a brief daily survey, we will capture the dynamic changes in participant experience throughout the day and the associations between users' subjective experience and their reactions to/interactions with the PF and DSS devices. This will be the first use of EMA with decision support systems.

During each treatment condition, over the course of 2-3 days every two weeks, the participant will be asked to complete a "Daily Diary" with 3-5 entries of 3-4 questions each day, for a minimum total of 48 entries per participant during each Phase.

The DiAs phone will display a text message containing a link to the survey. Surveys will be triggered at fixed times, including a morning survey ~1h after waking up and an end-of-the-day survey around 8-9 PM. Participants will be able to delay (up to 30 min) or skip (up to 2 per day excluding at wake up) surveys for their convenience.

Participants will respond to questions on a 5-point Likert scale (0=Not at All, 4=Extremely). The first Diary for each day will contain two additional items for rating sleep quantity/quality.

The Daily Diary questions are shown below and are intended to assess agreement, trust, treatment satisfaction, diabetes burden, self-efficacy, mood valence, energy level, and physical well-being.

- Quality of Life Parameters
  - At this moment, to what extent do you feel...
    - Burdened by your diabetes treatment?
    - Worried about your blood sugar levels?
    - In a positive or good mood?
    - Physically well?
- Sleep Items (only presented in the first Diary for each day)
  - Was your sleep last night…
    - Long enough?
    - Restful enough?
- Technology acceptance (only presented in the last Diary for each day)
  - Today to what extent have you...
    - Found (name of program) easy to use?
    - Found (name of program) useful?
    - Trusted the information given by (name of program)?
    - Found (name of program) easy to use?
    - Found (name of program) useful?
    - Trusted the information given by (name of program)?

9.13. Questionnaire Schedule

Timing	Escalation	De-escalation
Visit 1 – Screening and Questionnaires	Diabetes Specific Personality Questionnaire ABACUS Diabetes Locus of Control Confidence in Diabetes Self-Care Scale Clarke's Hypoglycemia Awareness Scale	
Visit 2 – Study Equipment Training	None	
Final week of SAM Run-in	T1-Diabetes Distress Scale Hypoglycemia Fear Survey Hyperglycemia Avoidance Scale	
Visit 3 Eligibility Assessment, Randomization and Training	Pittsburgh Sleep Quality Index	Pittsburgh Sleep Quality Index Technology Expectations (burdens subscale only) INSPIRE
DiAs Use in Phase 1 Mode	EMA Surveys	EMA Surveys
Week 7 of DiAs Use in Phase 1 Mode	Pittsburgh Sleep Quality Hyperglycemia Avoidance Scale	Technology Acceptance (burdens subscale only) Pittsburgh Sleep Quality Index T1-Diabetes Distress Scale
Week 8 of DiAs Use in Phase 1 Mode	Confidence in Diabetes Self-Care T1-Diabetes Distress Scale Hypoglycemia Fear Survey	Hypoglycemia Fear Survey Hyperglycemia Avoidance Scale Confidence in Diabetes Self-Care Scale
Visit 4 Phase 2 Initiation	Technology Expectations (burdens subscale only) INSPIRE (revised for DSS)	Technology Expectations (burdens subscale only) INSPIRE (revised for DSS) Diabetes Locus of Control
DiAs Use in Phase 2 Mode	EMA Surveys	EMA Surveys
Week 7 of DiAs Use in Phase 2 Mode	Technology Acceptance (burdens subscale only) Pittsburgh Sleep Quality Index T1-Diabetes Distress Scale	
Week 8 of DiAs Use in Phase 2 Mode	Hypoglycemia Fear Hyperglycemia Avoidance Scale Confidence in Diabetes Self-Care Scale	
Visit 5 Phase 3 Initiation	Technology Expectations (burdens subscale only) INSPIRE (revised for DSS) Diabetes Locus of Control	INSPIRE (revised for DSS) Diabetes Locus of Control
DiAs Use in Phase 3 Mode	EMA Surveys	EMA Surveys
Week 7 of DiAs Use in Phase 3 Mode	Technology Acceptance (burdens subscale only) to assess patients' experienced burdens related to the use of DSS Pittsburgh Sleep Quality Index (PSQI) to assess whether DSS improves sleep quality and quantity.	Pittsburgh Sleep Quality Index T1-Diabetes Distress Scale
Week 8 of DiAs Use in Phase 3 Mode	Hypoglycemia Fear Survey Hyperglycemia Avoidance Confidence in Diabetes Self-Care Scale	Hypoglycemia Fear Survey Hyperglycemia Avoidance Scale Confidence in Diabetes Self-Care Scale
Visit 6 Study Exit	ABACUS INSPIRE (revised for DSS) Diabetes Locus of Control	ABACUS

Chapter 10 Risks, Benefits, and Risk Assessment

10.1. Potential Risks and Benefits of the Investigational Device

Risks and Benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with T1DM and participants will be monitored for these symptoms.

10.1.1. Venipuncture Risks

A hollow needle will be placed in the arm for taking blood samples. Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

There is the risk of contamination from blood sampling techniques. Hand washing with either soap & water or waterless hand sanitizer will be used prior to caring for the study subject. Gloves will be worn during blood sample collection and processing. Medical personnel will continue to practice hygiene for the subject's protection (i.e. hand washing, changing gloves frequently, disposing needles properly). Gloves will be removed and hands washed or sanitized prior to leaving and upon return to the subject's room. Soiled linen will be changed to minimize the transfer of pathogenic organisms.

10.1.2. Fingerstick Risks

About 2 drop of blood will be removed by fingerstick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

10.1.3. Subcutaneous Catheter Risks

Participants using the study pump infusion sets will be at low risk for developing a local skin infection at the site of the infusion set placement. Though approved for 3 days of use, if a catheter is left under the skin for more than 24 hours it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causing a bruise (1 in 10 risk).

10.1.4. Sensor Needle Risks

Participants using the continuous glucose monitor (CGM) with sensor will be at low risk for developing a local skin infection at the site of the sensor needle placement. Though approved for 10 days of use, if a catheter is left under the skin for more than 24 hours it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causing a bruise (1 in 10 risk).

Study staff should verbally alert the participant that on rare occasions, the CGM may break and leave a small portion of the sensor under the skin that may cause redness, swelling, or pain at the insertion site. The participant should be further instructed to notify the study coordinator immediately if this occurs.

10.1.5. Risks of Hypoglycemia

As with any person having T1DM and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and subsequently for a few days the participant may not be as aware of symptoms of hypoglycemia. A poorly functioning CGM can periodically display falsely high glucose values, which could lead to inappropriate insulin recommendation.

10.1.6. Risks of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A poorly functioning CGM can periodically display falsely high glucose values, which could lead to inappropriate insulin recommendation.

10.1.7. Risks of Device Reuse

Participant will be informed that FDA or relevant national authorities have approved the insulin pump, CGM, glucometer and ketone meter for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study CGM system is labelled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter

is attached to the sensor but does not enter the skin and the receiver, if used, is a hand held device.

The study insulin pumps are labelled for single-patient use. During the study, this device may be reused after adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.).

10.1.8. Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Whenever the skin is broken there is the possibility of an infection. The CGM and pump infusion sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is indicated for use. Therefore, participants will be carefully instructed about proper use of the sensor.

10.2. Potential Benefits

It is expected that this protocol will yield increased knowledge about using a Decision Support System for insulin dosing suggestions. The individual participant may or may not benefit from study participation.

10.3. Risk Assessment

Based on the facts that (1) adults with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves feedback and advice for insulin dosing that may increase the likelihood of hypoglycemia, and hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting. .

10.4. General Considerations

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

Whenever possible, data will be directly collected in electronic case report forms, which will be considered the source data.

Chapter 11 Device Cleaning Instructions

CGM cleaning instructions are provided in the Dexcom G4 PLATINUM (Professional) Cleaning and Disinfection manual (current edition). The transmitter will be cleaned with Clorox Healthcare® Bleach Germicidal Cleaner or any disinfectant product in a spray bottle containing a bleach solution of 6500 parts per million with the EPA registration number 56392-7. The transmitter will be submerged in this solution and then placed on an absorbent wipe or clean surface. Two sprays will be dispensed from the Clorox cleaner onto each side of the transmitter. A nylon brush will be used to scrub the transmitter on all sides for 30 seconds. The transmitter will be placed in the Clorox Cleaner solution for one minute. The transmitter is then rinsed under flowing tap water for ten seconds. The transmitter will then be disinfected using a disinfectant product with EPA registration number 56392-7 using similar procedures as the cleaning process.

Per the pump manufacturer, the insulin pump will be cleaned with a damp lint-free cloth. Use of household or industrial cleaners, solvents, bleach, scouring pads, chemicals, or sharp instruments are prohibited. The pump should never be submerged in water. If needed, a very mild detergent, such as a bit of liquid soap with warm water will be used. A soft towel will be used to dry the pump.

Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. Cavicide, EPA number 46781) or household bleach. The contact time on the surface depends on the method used to clean the equipment. Cavicide requires three minutes on the surface of the equipment. Clorox Germicidal Bleach Wipes require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with the disinfectant to be considered effective though not wet enough to leave drops of liquid.

In the event a manufacturer update for cleaning procedures of their device, the study team will adhere to the most current recommendations.

Chapter 12 Adverse Events, Device Issues, and Stopping Rules

The protocol is considered a significant risk device study due to the fact that the closed loop system is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

12.1. Definitions

12.1.1. Adverse Events (AE)

A reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

- A Serious Adverse Event as defined in section 12.1.2
- An Adverse Device Effect as defined in section 12.1.4, unless excluded from reporting in section 12.8
- An Adverse Event as defined in section 12.1.4 occurring in association with a study procedure
- An AE as defined in section 12.1.1 which leads to discontinuation of a study device for 2 or more hours
- Hypoglycemia meeting the definition of severe hypoglycemia as defined in section 12.3.1
- Diabetic ketoacidosis (DKA) as defined in section 12.3.2 or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

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

12.1.2. 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 inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (life threatening).
- Is a congenital anomaly or birth defect.

- 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).

12.1.3. Unanticipated Adverse Device Effect (UADE)

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

12.1.4. Adverse Device Effect (ADE)

Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed.

12.1.5. Device Complaints and Malfunctions

A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3).

12.2. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practices (GCP), or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented as appropriate. Major deviations will be reported to the IRB-HSR within 7 calendar days of when the study team becomes aware of the event.

12.3. Reportable Events

12.3.1. Hypoglycemia Event

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met:

- The event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions;
- Impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma;
- If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

12.3.2. Hyperglycemia Events/Diabetes Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following four criteria is met.

The event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below:

- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- Blood ketone level ≥1.5 mmol/L and communication occurred with a health care provider at the time of the event
- Blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider
- Hyperglycemic events are classified as DKA if the following are present:
    - Symptoms such as polyuria, polydipsia, nausea, or vomiting;
    - Serum ketones ≥1.5 mmol/L or large/moderate urine ketones;
    - Treatment provided in a health care facility

All reportable Adverse Events—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an adverse event form online. Adverse events will be presented to the DSMB in accumulated manner during each meeting.

12.4. Relationship of Adverse Event to Study Device

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

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

- There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.
- Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

12.5. Intensity of Adverse Event

The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- **MILD:** Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- **MODERATE:** Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- **SEVERE:** Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

12.6. Coding of Adverse Events

Adverse events will be coded per the UVA IRB website instructions (i.e. mild, moderate, severe). Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

12.7. Outcome of Adverse Events

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

- **RECOVERED/RESOLVED** – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.

- **RECOVERED/RESOLVED WITH SEQUELAE** – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- **FATAL** – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- **NOT RECOVERED/NOT RESOLVED (ONGOING**) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
- An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
- The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- **UNKNOWN** – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

12.8. Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labeling
- CGM tape adherence issues

- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that do not meet criteria for AE reporting

12.9. Timing of Event Reporting

- UADEs must be reported within 10 working days to the FDA after the sponsor first receives notice of the adverse effect.
- Other reportable adverse events, device malfunctions (with or without an adverse event) and device complaints should be reported promptly, but there is no formal required reporting period.
- The IDE Sponsor will investigate the UADE and if indicated, report the results of the investigation to the IRBs, FDA, and DSMB will within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b).
- The DSMB will determine if the UADE presents an unreasonable risk to participants. If so, the DSMB will must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the DSMB will makes this determination and no later than 15 working days after first receipt notice of the UADE.
- In the case of a device system component malfunction (e.g. pump, CGM, control algorithm), information will be forwarded to the responsible manufacturer by the study personnel.

12.10. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be establish to review compiled safety data at periodic intervals to oversee and monitor our randomized clinical trial to ensure the safety of participants, as well as the validity and integrity of the data.

Details regarding membership, meetings, responsibilities will be documented in a separate DSMB Charter.

12.11. Stopping Criteria

12.11.1. Participant Discontinuation

Rules for discontinuing study device use are:

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Two distinct episodes of DKA
- Two distinct severe hypoglycemia events as defined in section 12.3.1

12.11.2. Suspending/Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event, use of the study device system will be suspended while the problem is diagnosed.

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

12.12. Independent Safety Oversight

A Medical Monitor will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The Medical Monitor can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding Medical Monitor review will be documented in a separate Medical Monitor document.

Chapter 13 Miscellaneous Considerations

13.1. Prohibited Medications, Treatments, and Procedures

Participants using glulisine at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to lispro or aspart for the duration of the trial.

The study devices (study insulin pump, study CGM) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above.

13.2. Participant Withdrawal

Participation in the study is voluntary. Participant may withdraw at any time. For participants who do withdraw from the study, the study team will determine if their data will be used in analysis.

13.3. Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study may be shared with the third-party collaborators. De-identified subject information may also be provided to collaborators involved in the study after the appropriate research agreement has been executed.

Chapter 14 Statistical Consideration

14.1. Design and Randomization

This is a randomized crossover study in T1DM designed to demonstrate the efficacy of personalized feedback (PF) and decision support (DSS) over sensor-augmented pump (SAM) therapy and to establish relationships between the level of glucose variability (GV) control achievable by the intervention and individual psycho-behavioral characteristics.

We plan to split the study into 4 cohorts of about 25 participants each (expected retention 20 per cohort). Each cohort will continue for ~7 months and will have the structure presented in Figure 5. Following recruitment, screening, and a run-in period of SAM, participants will be randomized into one of two groups: escalation vs. de-escalation of devices and function. Each treatment modality (SAM, PF, DSS) will continue for about 8 weeks, with the last 4 weeks used to assess GV from CGM data.

Escalation: SAM → PF → DSS

De-escalation: DSS → PF → SAM

14.2. Sample Size

14.2.1. Sample Size Determination:

Sample size determination is based on our related pilot studies of DSS. We estimate that the effect size of DSS vs. SAM will be $f^3$0.22. Power calculations (G*Power 3.1.9.2) assuming a=0.017 (corrected for multiple comparisons), 95% power, correlation of 0.55 between the repeated measures, and attrition of 20%, yield a sample size of N=100 subjects to be randomized at baseline, with N=80 subjects completing the study. PF vs. SAM assumes the same effect size. We expect that while overall DSS effect vs. PF will be smaller than vs. SAM, GV control over time will be more consistent. Aim 1.3 analysis therefore assumes a small effect size (0.15) but 5 repeated measures (bi-weekly) in each condition with higher correlation (0.65), leading to an achieved power of 97.2% for this Aim.

14.2.2. Exploration of the effect of treatment escalation vs. de-escalation:

A key advantage of the proposed study design (beyond the optimal statistical power) is the possibility to explore the glucose control and psycho-behavioral impact of features being added and/or enhanced with prescriptive components (DSS), vs. features being limited to information (PF) or even removed (SAM). We will perform this analysis by looking at the between factors in the repeated ANOVA analysis, contrasting the escalation group vs. de-escalation group. While

not powered, this analysis will provide key insights in the future feature adaptation schemes based on the ATI.

14.3. Outcome Measures

14.3.1. Glycemic outcomes:

The primary outcome of this study will be Glucose Variability (GV) as measured by CGM-based Coefficient of Variation (CV), as recommended by the International Consensus on Use of Continuous Glucose Monitoring. To further characterize glucose control, we will compute other CGM Consensus outcomes as well:

- Average
- Percent in different ranges:
  - <50 mg/dL
  - <54 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - ≤70-≤180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- SD and coefficient of variation
- LBGI, HBGI, ADRR

Each modality of treatment will be assessed using the last 4 weeks of CGM recordings, as we expect most of the GV benefits of each intervention to be realized within the first 4 weeks of the intervention, and a minimum of 24 days of data is considered optimal for CGM–based CV determination.

14.3.2. Glucose Variability Reduction Achieved with CGM-based expert systems:

General linear models (GLM) (repeated measures ANOVA) will be used to assess the significance of the differences in average response between SAM, PF, and DSS across appropriate CGM-based metrics. The particular design of the clinical study allow for Aims 1.1, 1.2, and 1.3 to each be addressed independently in a randomized crossover analysis, as shown in Figure 4. While the randomized order of the interventions (escalation vs de-escalation) allows for an objective assessment of the average efficacy of each of them, we will introduce the order as a fixed factor to verify if significant study effects can be detected. Finally, we will study the evolution of GV within each modality period: GV and other CGM-based outcomes will be computed bi-weekly (the minimum length of time for precise GV assessment) and entered in a repeated measures

GLM analysis; within-subject contrast (linear and polynomial) using 5 repeated measures per condition to explore the evolution of the glycemic outcomes in time; Aim 1.3.

14.4. Exploration of the effect of treatment escalation vs. de-escalation

A key advantage of the proposed study design (beyond the optimal statistical power) is the possibility to explore the glucose control and psycho-behavioral impact of features being added and/or enhanced with prescriptive components (DSS), vs. features being limited to information (PF) or even removed (SAM). We will perform this analysis by looking at the between factors in the repeated ANOVA analysis, contrasting the escalation group vs. de-escalation group. While not powered, this analysis will provide key insights in the future feature adaptation schemes based on the ATI.

14.5. Psychological and Behavioral Questionnaires

Quantitative data on usability and satisfaction will be analyzed using simple descriptive statistics. In addition, we will analyze scores from the measures in the psychosocial assessment battery to determine if changes occur over time and between groups. Using SPSS 26, we will construct predictive models in the general linear modeling (GLM) framework to examine each set of psychological factors (e.g., INSPIRE survey) over time, and their association with glycemic outcomes. Group assignment and Study Phases will be the primary covariate.

14.6. Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed overall and by treatment group.

Will include:

- Age
- HbA1c collected at randomization and study end
- Gender
- Race/ethnicity
- CGM use before enrollment
- Diabetes duration
- BMI

14.7. Device Issues

We will count each time the participant interacted with the study Personalized Feedback and Decision Support System and perform a Wilcoxon paired rank test to determine if any differences exist in system interactions.

Chapter 15 Data Collection and Monitoring

15.1. Case Report Forms and Device Data

The study data are collected through a combination of case report forms (electronic and paper) and electronic device data files obtained from the software and individual hardware components. These electronic device files and electronic CRFs are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Records will be maintained in accordance with ICH E6 and institutional regulatory requirements for the protection of confidentiality of participants.

15.2. Study Records Retention

Study documents will be retained for a minimum of 2 years after study close out. These documents may be retained for a longer period, however, if required by local regulations. No records will be destroyed without the consent of the Principal Investigator. It is the responsibility of the Principal Investigator to inform all co-investigators when these documents no longer need to be retained.

Chapter 16 Ethics/Protection of Human Participants

16.1. Ethics Standard

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

16.2. Institutional Review Boards

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

16.3. Informed Consent Procedures and Documentation

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

The participant will sign the informed consent document prior to any procedures being done specifically for the study. A copy of the informed consent document will be given to the participant for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

16.4. Participant and Data Confidentiality

The study monitor, representatives of the IRB or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the University of Virginia Center for Diabetes Technology. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases may be de-identified and archived at the University of Virginia Center for Diabetes Technology.

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