Impaired Awareness of Hypoglycemia Consortium (IAHC)

Study Title: **C**losed **L**oop and **E**ducation for hypoglycemia **A**wareness **R**estoration (CLEAR)

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A. Study Objectives

The purpose of this study is to determine the effect on counterregulatory responses (CRR) of intervening (by attempting to strictly avoid hypoglycemia) to improve awareness of hypoglycemic symptoms among adults with type 1 diabetes (T1D) who have impaired awareness of hypoglycemia (IAH). IAH affects 20-25% of adults with T1D, and rises with increasing duration of T1D (1, 2).

Individuals with IAH exhibit blunted symptomatic and CR hormonal responses to hypoglycemia and, as such, have an impaired ability to respond to hypoglycemia. Thus, rates of severe hypoglycemia are up to 6-fold greater in those affected. Intensive management of T1D is necessary in preventing long-term complications, but can be complicated by recurrent episodes of hypoglycemia which lead to and sustain the CRR deficits of IAH. Technologies such as continuous glucose monitoring (CGM) and hybrid closed-loop (HCL) systems can reduce severe hypoglycemia (and also may reduce IAH) but the ability of technology to reverse impaired CRR (as assessed with experimental hypoglycemia clamp) remains unclear. Behavioral and psycho-educational interventions targeting knowledge/skills gaps, as well as particular cognitions and behaviors driving recurrent hypoglycemia, can also reduce severe hypoglycemia and improve awareness. No studies have compared technology with such behavioral interventions in terms of assessing their impact on IAH or the CRR (as a primary outcome). Unanswered questions include the degree of reduction in hypoglycemia required to restore awareness. Furthermore, participants may respond to different interventions according to their characteristics (3, 4). For example, it remains unclear whether older individuals benefit from such interventions since they usually are excluded from studies. Therefore, there is an urgent need to determine effective interventions that can reverse IAH in a large representative population of adults with T1D and IAH. We propose to study the effect of specific interventions aimed at restoring

- the CRR (tested via an experimental hypoglycemia clamp procedure)
- hypoglycemia awareness (self-reported via the Towler Questionnaire (5) during the experimental hypoglycemia clamp procedure)

The study will use a Sequential Multiple Assignment Randomized Trial (SMART) design. At baseline, all participants who are HCL naïve will be randomized to HCL or Usual Care (UC) plus brief education (My HypoCOMPaSS) with a follow-up of two years. UC will consist of real-time continuous glucose monitoring (CGM) and insulin delivery via pump or multiple daily injections. Participants who fail to increase their CRR at 12 months will be randomized, or assigned, to a second intervention consisting of a small-group educational program focusing on motivations and unhelpful cognitions acting as barriers to hypoglycemia avoidance (HARPdoc). At baseline, all participants who are HCL non-naïve will be randomized to optimized HCL or HCL plus My HypoCOMPaSS; those with non-responsive CRR at 12 months will be randomized to either continue HCL (on the basis they need a longer period to reverse impaired CRR and total symptomatic responses) or to the HARPdoc intervention. Participants randomized to an HCL device are expected to wear the device continually, as well as a CGM. The My HypoCOMPaSS education requires 4-5 hours of training, whereas, the HARPdoc education requires four training sessions of seven hours each during weeks 1,2,3, and 6.

The specific aims and hypotheses are as follows:

Aim 1: To determine the effect on CRR (epinephrine increase ≥ 125 pg/ml over baseline) and total symptom responses (Towler Questionnaire increase ≥ 20% over baseline) during a hyperinsulinemic-hypoglycemic clamp procedure (glucose < 50 mg/dl) after 12 months of HCL versus Usual Care plus My HypoCOMPaSS Educational Intervention among adults with T1D and IAH who have never used HCL therapy previously.

Hypothesis 1: At 12 months, those allocated to Usual Care plus My HypoCOMPaSS will be more likely to have improved CRR and total symptomatic responses than those allocated to HCL.

Aim 2: To determine the effect on CRR and total symptom responses at 12 months of HCL plus My HypoCOMPaSS versus HCL alone among adults with T1D and IAH who are currently using HCL therapy prior to entering the study.

Hypothesis 2: At 12 months, those allocated to HCL plus My HypoCOMPaSS will be more likely to have improved hypoglycemic awareness and improved CRR than those using HCL alone.

Aim 3: To determine the durability of effect over 24 months of the intervention that improves CRR at 12 months among adults with type 1 diabetes and IAH at baseline.

Hypothesis 3: At 24 months, CRR will improve further among those who had restored CRR at 12 months.

Aim 4. To determine the effect on hypoglycemic awareness (Towler Questionnaire increase ≥ 20% over baseline) and CRR (epinephrine increase ≥ 125 pg/ml over baseline) during a hyperinsulinemic hypoglycemic clamp procedure at 24 months of an in-depth educational program (HARPdoc), initiated throughout months 12-24, among adults with T1D and IAH at baseline, for whom the intervention allocated at baseline did not restore CRR at 12 months.

Hypothesis 4: At 24 months, those allocated to HARPdoc for months 12-24 months will be more likely to have improved hypoglycemic awareness and CRR than those who continue with the therapy allocated at baseline.

B. Outcomes

The primary outcome is a composite of the rise in epinephrine and the rise in self-reported total symptom scores during experimental hypoglycemia compared to the initial scores measured at euglycemia. Participants who show a positive response at 12 months as compared to baseline during the clamp studies will be deemed as having improved awareness of hypoglycemia (6). A response at 12 months will be assessed as positive if the peak epinephrine response is 125 pg/ml greater than at baseline, and if the autonomic symptom scores are 20% greater than at baseline.

Secondary outcomes include an assessment of changes at 12 months and at 24 months in the following measures:

1. Additional CRR hormone/metabolite responses to experimental hypoglycemia during the clamp study [glucagon, pancreatic polypeptide, free fatty acids, glucose infusion rate]
2. Total symptom scores during the clamp study via the Towler Questionnaire (5)
3. CGM parameters during the four weeks before each clamp study [for example, % of time with sensor hypoglycemia <70 mg/dL/ <54 mg/dL, the number of hypoglycemia episodes defined as ≥ 15 minutes below the respective thresholds, % time with sensor glucose in range (70 to 180 mg/dL), >180 mg/dL/ >250 mg/dL, CGM coefficient of variation and % of time CGM use was reported in an average numbers of days per week, and the glycemia risk index (GRI)]
4. Cognitive function during the hyperinsulinemic-hypoglycemia clamp procedure [trail making B, four-choice reaction time and an interoceptive task]
5. Awareness of hypoglycemia assessed on the day of or before each clamp study:
    a. Gold (7)
    b. Clarke (8)
    c. DAFNE UK Score (9)
    d. HypoA-Q (10)
    e. Hypo-METRICS (only item 27 – hypoglycemia event or prevention) (11)
6. Laboratory parameters [HbA1c]
7. Hypoglycemia-specific Person-Reported Outcome Measures (PROMs) measured during the two weeks before each clamp study:
    a. Hypo-METRICS (11)
    b. Hypoglycemic Confidence Scale (HCS) (12)
    c. Hypoglycemia Fear Survey-II (HFS-II) (13)
    d. Attitudes to Awareness of Hypoglycaemia (A2A) Scale (14)
    e. Type 1 Diabetes Distress Scale (15)

f. Diabetes Self-Management Questionnaire (16)
g. Diabetes Management Experiences Questionnaire (17)
h. PROMIS Sleep Disturbance – Short Form 8a (18)
i. Hospital Anxiety and Depression Scale (19)
j. 12-Item Hypoglycemia Impact Profile (HIP12) (20)
k. EQ-5D-5L (21)

8. Symptoms of hypoglycemia via Hypo-METRICS during the four weeks before each clamp
9. Physiological variables (sleep duration and quality, 24-hour step count, exercise bouts, resting heart rate, heart rate during exercise, heart rate variability) during the two weeks before each clamp, assessed using a non-invasive physiological monitor
10. Severe hypoglycemia via the HypoA-Q [open and anonymous recall at 6-monthly contacts for months 0-24 which is annualized and annual rate months 12-24]
11. Adverse events and complications [adverse device effects, severe hypoglycemia, diabetic ketoacidosis (DKA), hospitalizations, ER visits, major adverse cardiovascular events (MACE), and all-cause mortality]

C. Background

People with type 1 diabetes (T1D) are at risk of complications that can be minimized by achieving near normal plasma glucose (22). However, iatrogenic hypoglycemia is a main limiting factor (23). On average, a person with T1D has two episodes of symptomatic hypoglycemia per week and one or more episodes of severe hypoglycemia, defined as requiring third-party assistance per year (24, 25). Hypoglycemia causes negative biological, psychological, and social consequences (26). Indeed, as well as provoking substantial morbidity, hypoglycemia can be fatal (27, 28). Thus, hypoglycemia mitigates against people with T1D achieving glycemic targets. Repeated hypoglycemic events compromise physiological counter-regulatory responses (CRR) and behavioral defenses that normally would prevent severe hypoglycemia and/or subsequent episodes (29). A single episode of hypoglycemia attenuates sympatho-adrenal responses to subsequent hypoglycemia in healthy people (30) and those with T1D (31). Hypoglycemia of greater depth (32), longer duration (33), and higher frequency (32) results in greater attenuation of CRR to subsequent hypoglycemia. This phenomenon reduces an individual's ability to perceive the onset of hypoglycemia symptoms leading to impaired awareness of hypoglycemia (IAH) (34). Clinical IAH is heterogenous and progresses continuously, from early loss of autonomic symptoms, followed by a reduction in the number and intensity of hypoglycemia symptoms, and, rarely, total absence of symptoms related to hypoglycemia (34). Based on validated questionnaires, the reported prevalence of IAH is 20-25 % in T1D and rises to ~50 % after ≥25 years of disease duration (1, 2). IAH increases the risk of severe hypoglycemia in T1D by a factor of 6-to-20-fold (7, 35). This is because the loss of symptoms is compounded by a reduction in glycogenolysis, which arises from a failure of glucagon secretion and a progressive blunting of epinephrine responses, which together remove both the drive to take corrective action as glucose falls as well as the endogenous CRR processes which counteract the glucose lowering effect of insulin.

Studies conducted in the 1990s, aimed at reversing IAH, demonstrated that meticulous avoidance of hypoglycemia for as little as 2-3 weeks improves awareness and autonomic symptoms, but this occurs without a consistent improvement in CRR hormone responses, particularly epinephrine, suggesting that sympathoadrenal responses to hypoglycemia remain impaired (36-38). Clinical pathways for managing problematic hypoglycemia in IAH have focused on avoiding hypoglycemia through education, technology, psycho-behavioral interventions, and islet cell transplantation (39). The only intervention that has demonstrated robust restoration of awareness and improved symptom and CRR hormones is islet cell transplantation (40). Whilst effective, islet cell transplantation is limited by expertise confined to specialized University centers, costs of commercialization in the United States, availability of donor pancreas and the need for life-long immunosuppression (41). Technological developments in the last decade, including continuous glucose monitoring (CGM) and hybrid closed-loop (HCL) systems, have demonstrably reduced the burden of hypoglycemia, raising hopes that they can reverse IAH. Real-time CGM lowers the incidence of hypoglycemia in those with IAH including severe events (42-44). However, recent observational data suggest that whilst the overall incidence of severe hypoglycemia declines with CGM, there is a significant (up to 6-fold) persistent

residual risk of severe hypoglycemia with persistent IAH despite CGM use compared to those without long-term CGM use (45). Without restoration of physiological awareness, those with IAH treated with CGM remain at risk when they are not using sensors and there are many cases of severe hypoglycemia that happen when sensors are not active. Data on improved physiological awareness of hypoglycemia on self-reported questionnaires following CGM are not convincing and confounded by the presence of alerts and alarms designed to prevent hypoglycemia, with an improvement in some but not all cohorts (6, 46). Assessment of CRR to experimental hypoglycemia before and after CGM use in T1D with IAH are limited by the small number of participants studied (n=33) but suggest only a modest improvement in epinephrine or autonomic symptom responses. Overall, CGM use has not been shown to convincingly reverse IAH in a large population with T1D and estimates suggest between 30-80% of individuals on CGM have persistent IAH. This may be due to reduced accuracy of CGM systems under hypoglycemic conditions (47, 48) meaning not all episodes of hypoglycemia are scrupulously avoided, and alarms, particularly overnight, may not be perceived by the CGM user. It also is unknown what CGM metrics (the extent to which maintenance of time in range (TIR) 70 to 180 mg/dL and near-complete avoidance of time below range <70 mg/dL and <54 mg/dL) are necessary to restore awareness of hypoglycemia measured by self-reported questionnaires and improved CR.

HCL systems are a further step towards hypoglycemia reduction (49) and represent state-of-the-art in T1D care. HCL systems consist of CGM, an insulin pump, and an algorithm that automatically modulates insulin delivery based on CGM sensor interstitial glucose values. HCL systems thus increase insulin delivery when the sensor glucose is predicted to be high and decrease insulin delivery when sensor glucose is predicted to be low, and so are designed to help maintain time in range. Current technology is classified as hybrid, as people with T1D still need to manually bolus insulin for carbohydrates. There are six main systems currently used across different countries:

- Tandem t:slim x2™ with Control iQ algorithm
- Omnipod® OP5 with Smarttcontrol
- Ypsopump/Dana pump with CamAPS Fx algorithm
- Beta Bionics iLet Bionic Pancreas
- Medtronic 780G
- Tidepool Loop

These systems all have demonstrated safety and efficacy in T1D, reducing time in hypoglycemia and improving time in range and HbA1c, vs sensor-augmented (open loop) pumps, which can receive data from CGM but still require manual insulin dosing. Pilot data from short duration (≤ 8 weeks) studies investigating HCL systems in those at high risk of hypoglycemia (n=45) (50) and/or with IAH (n=17) (51) show hypoglycemia reduction but no improvement in sympatho-adrenal epinephrine and only modest improvement in autonomic symptom responses to experimental hypoglycemia (52). A pilot study of long-term HCL intervention in individuals with type 1 diabetes and IAH did demonstrate an improvement in the epinephrine response to experimental hypoglycemia after 6-months with further improvement by 18-months and parallel incremental improvement in the pancreatic polypeptide and autonomic symptom responses during hypoglycemic clamp testing (53). A large study in IAH patients using a predictive low suspend system showed significant reduction in hypoglycemia, but no change in Gold scores over 6 months (54). It is critical now to determine if long-term HCL can restore awareness of hypoglycemia through improved CRR and self-reported questionnaires through avoidance of hypoglycemia whilst optimizing TIR and HbA1c, in a large adult population with T1D and IAH who are naïve to HCL therapy as well as those already using HCl.

The observation that IAH can persist in people with T1D already using HCL suggests that additional factors contribute to persistent IAH and hypoglycemic risk which need to be addressed by other approaches. Strong candidates include educational or behavioral interventions since they also have been shown to reverse IAH (55).

The HypoCOMPaSS trial recruited adults with T1D and IAH, randomized in a 2 × 2 factorial design to CGM, insulin pumps or multiple daily injections (MDI) alone. All participants received brief (1-2 hours) of standardized education individually or in small groups with the goal of optimizing hypoglycemia recognition and immediate action to prevent significant events through a structured curriculum identifying personalized strategies for hypoglycemia prevention, detection and management without ‘relaxing’ overall glucose ‘control’. This was designed to be used in

support of a multimodality intervention in parallel with optimized glucose monitoring and insulin delivery. It was followed by weekly support from research fellows to review individualized strategies and encourage protocolized insulin dose reductions in response to biochemical hypoglycemia. At 6 months, time spent with glucose <54mg/dl was reduced while remaining significant (1.5%). IAH had improved in all groups and rates of severe hypoglycemia fell from 77% of individuals in the 6 months before the trial to 20%, without deterioration in HbA1c (56). Benefits including improved hypoglycemia awareness persisted for 2 years in parallel with significant reduction in HbA1c (pre-study, 8.2% vs. post-HypoCOMPaSS 7.7%) (57) . In 18 participants who underwent paired hyperinsulinemic hypoglycemic clamp studies before study and at 6 months, glucose thresholds for symptoms increased from 47 mg/dl to 56 mg/dl in parallel with recovery of metanephrine response to hypoglycemia, while threshold for impaired cognitive function remained unchanged at 50 mg/dl (58).

Cognitive factors, specifically unhelpful health beliefs around hypoglycemia, can also modulate hypoglycemia risk and awareness of hypoglycemia. Neuroimaging studies (59) investigating brain response to acute experimental hypoglycemia in those with T1D with and without IAH showed different changes in brain regions involved in arousal, decision making, emotion, memory, and reward (as well as those involved in generating and perceiving stress responses) in IAH (60). People with IAH describe thoughts (cognitions) and attitudes that act as barriers to hypoglycemia avoidance. These studies suggest the possibility that the loss of these individuals' ability to recognize and effectively manage hypoglycemia may be sustained, at least in part, by loss of motivation, so that hypoglycemia risk behaviors continue. This may partly explain persistent IAH in a small but highly vulnerable group of people, who may maintain risk behaviors that could even undermine HCL (61). This group of people is highly vulnerable not just because of problematic hypoglycemia – they also have high rates of anxiety and depression (61). The Hypoglycemia Awareness Restoration Programme for adults with type 1 diabetes and problematic hypoglycemia despite optimized self-care (HARPdoc) is a novel program. It uniquely addresses cognitive barriers to hypoglycemia avoidance and is delivered in small group format over 6 weeks by trained educators with support from a clinical psychologist, using psychological theory (motivational interviewing and cognitive behavioral theory). It has been assessed in a formal RCT against Blood Glucose Awareness Training (BGAT) in T1D with treatment-resistant IAH (62). HARPdoc is distinct from BGAT because of its cognitive and psychotherapeutic elements. In the trial, HARPdoc was superior to BGAT in reducing both endorsement of unhelpful cognitions and mental health scores for diabetes distress, anxiety and depression, while both interventions improved hypoglycemia awareness and reduced high baseline rates of severe hypoglycemia. Participants in the trial had all had prior structured education in flexible insulin therapy and access to technology, although many had stopped or had not tried using technology at recruitment. The potential of such a program to restore awareness of hypoglycemia through improved CR responses and self-reported questionnaires in those whose IAH has persisted, despite being established on HCL, needs further investigation.

A key limitation common to randomized clinical trials (RCT) investigating interventions to reduce hypoglycemia in T1D is exclusion of participants with IAH. Trial participants have not been comprehensively phenotyped. Thus, it is unclear to what extent factors such as age, sex, duration of diabetes, diabetes complications, residual endogenous insulin/C-peptide, recent severe hypoglycemia and antecedent hypoglycemia contribute to individuals' ability to regain awareness following intervention. This matters because different pathophysiological defects causing IAH may respond differently to each of the planned interventions. Targeted interventions could achieve greater success. Older adults (>70 years) with T1D and IAH are particularly underrepresented in current studies. Older adults with T1D have high prevalence of IAH (23), cognitive impairment (63) and physical frailty (64) [1], all of which increase hypoglycemia risk. HCL systems may reduce the cognitive burden of day-to-day diabetes management in older people. Learning new skills in using technology and then deploying them for self-management may however create additional cognitive demands. Whether older people naïve to HCL will improve IAH with HCL, and whether older people with persistent IAH (despite using technology) benefit from adjunctive psycho-educational intervention, need investigation.

Another challenge is that questionnaires developed by Gold (7) and Clarke (8), widely used in research and practice to define IAH, and developed and validated before the advent of novel technologies are limited by not being 1) able to identify patient characteristics that predict successful restoration of awareness, or 2) able to distinguish

subjective from sensor-driven hypoglycemia awareness. Newer self-reported measures such as the DAFNE UK Score (9) (which asks participants whether they usually recognize their hypoglycemia at, or above, a glucose measure of 54 mg/dl, or not at all) and the hypoglycemia awareness questionnaire (HypoA-Q) have promise (10). This latter questionnaire requires further evaluation in a large adult population with T1D and IAH to determine its ability to adequately identify impaired awareness and predict restoration of awareness by correlating this with CRR. Combining self-report with CGM metrics of hypoglycemia exposure and risk is another approach. It has been validated for the Clarke score, which measures hypoglycemia experience as awareness and frequency of severe episodes, that when combined with time-below-range identifies individuals with an absent autonomic symptom response to hypoglycemic clamp testing (65). Furthermore, it is increasingly recognized that improving glycemia metrics with technology may not necessarily translate to improved patient experience (66). Benefits from technology such as HCL may be eroded by factors including mistrust of automation, technical glitches that overwhelm the person with diabetes, difficulties incorporating technology into everyday life, and distress, anxiety and depression from constantly carrying a 'reminder' of T1D. Research is therefore needed to explore effects of HCL on psycho-social factors and quality of life (QoL) using patient reported outcome measures (PROMs) in a diverse group of adults with T1D and IAH. The HypoMETRICS app, developed as part of the HypoMETRICS study, allows collection in real time using a technique called Ecological Momentary Assessment (EMA) of the experience of hypoglycemia, including the intensity and nature of symptoms experienced [https://pubmed.ncbi.nlm.nih.gov/36930585/; https://pubmed.ncbi.nlm.nih.gov/35105572/]. Its use will allow us to track the proportion of sensor-detected hypoglycemia events for which the participant experienced symptoms, and also any changes in the nature and intensity of symptoms as a way of detailed evaluation of awareness status in real time.

In the My HypoCOMPaSS trial, anxieties related to high glucose levels and avoidance behaviors, which may increase risk of hypoglycemia, were assessed using the Hyperglycemia Avoidance Survey (67). Scores in all sub-scales were lower at study completion reflecting reduced 'worry' regarding high glucose levels, attenuated 'low blood glucose' preference, less 'avoidance of glucose extremes' and lower drive to take 'immediate action' for high glucose levels (68). In addition, as measured by the Attitudes to Awareness questionnaire (67), improvements were observed in both prioritizing avoidance of hyperglycemia (whole cohorts score at baseline: 5.3 ± 2.3 vs. 6 months: 4.3 ± 2.3; P=0.001) and 'normalizing asymptomatic hypoglycemia' (baseline: 1.5 ± 1.9 vs. 6 months: 0.8 ± 1.2; P=0.039) were also reduced following the intervention (data in preparation for publication). In a pilot RCT comparing the My HypoCOMPaSS educational intervention alone with standard care in a cohort of 24 participants with T1D and IAH, the Hyperglycemia Avoidance Survey revealed significant improvements in drive to immediately act in response to high glucose (baseline score: 8.3 ± 3.9 vs. 6 months: 6.1 ± 4.4; P=0.01) and worry about high glucose (baseline: 26.2 ± 11.8 vs. 6 months: 19.6 ± 11.4; P=0.02) in those randomized to the educational program (data in preparation for publication).

The HARPdoc program targets cognitions around hypoglycemia that act as barriers to hypoglycemia avoidance and recovery of awareness using motivational and cognitive approaches, delivered by diabetes educators, trained and supported by a clinical psychologist, in small group format. Published data in a trial conducted in people with IAH and severe hypoglycemia that was persisting despite exposure to structured education and access to technology show that, while HARPdoc was not superior to a non-cognitive intervention (BGAT) in reducing severe hypoglycemia and improving awareness scores (successfully achieved with both interventions), HARPdoc uniquely improved scores on mental health measures (diabetes distress, general anxiety and depression), as well as improving scores on cognitions. Further preliminary data show improvements in quality of life (EQ-5D-5L scores) in, and reduced use of a wide range of community and hospital-based health services by, HARPdoc graduates, including hospital admissions, which conferred formal cost-effectiveness on the HARPdoc program, at least in the UK arm of the randomized trial. These observations were made over a follow-up period of 24 months (62). In an effectiveness-implementation study from the trial, participants rated HARPdoc highly, including feasibility and appropriateness, with higher scores being associated with the higher mental health scores (62).

Hybrid closed loop pumps are made by several companies and are available for use in the USA, United Kingdom, and Australia. CLEAR participants assigned to HCL pump thereby will select the device they will use during the study. It is expected that those participants on HCL prior to the study will continue with their current device. HCL naïve participants will be introduced to the HCL available in the country in which they reside and allowed to choose the device they plant to wear. Table C.1 lists the hybrid closed loop pumps we plan to use in the study. In each case, the pump uses a proprietary algorithm that adjusts the insulin infusion rate based on the glucose data collected from the CGM. As an example, the Tandem t:slim X2 insulin pump with Control-IQ Technology uses a control algorithm originally developed by the University of Virginia (69, 70). The Control-IQ HCL has been tested in an RCT comparing Control-IQ HCL with a sensor augmented pump (SAP) that suspends insulin delivery as glucose falls as part of the International Diabetes Closed-Loop (iDCL) trial funded by the NIH (71). This study recruited 168 participants with T1D (range, age 14 to 71 years, T1D duration 1 to 62 years, HbA1c 5.4 to 10.6 %) and randomized 112 participants to Control-IQ HCL and 56 participants to SAP. Participants were not phenotyped by awareness status and only 5% (n=5) in the closed-loop group had a severe hypoglycemic event in the year before enrollment. Also, 34% (n=38) in this group had a baseline HbA1c <7.0%. In this 6-month trial, the primary outcome was percentage of time that CGM glucose was in range (70 to 180 mg/dL) with a reduction in time <70 mg/dL a secondary outcome. The Control-IQ HCL resulted in a significant improvement in percentage TIR (mean ± SD) 61 ± 17% at baseline compared to 71±12% at 6 months in the Control-IQ HCL group vs. an unchanged 59±14% TIR in the control SAP group (mean difference [closed loop minus control], 11 percentage points; 95% confidence interval [CI], 9 to 14; P<0.001). This mean difference equates to 2.6 more hours per day spent in range with Control-IQ HCL. **The Control-IQ algorithm also resulted in a significant reduction in CGM time in hypoglycemia <70 mg/dL compared with SAP (12 minutes per day reduction with closed-loop vs, SAP, P<0.001)**. In a recent, real-world retrospective analysis of Control-IQ HCL from 9,451 users who uploaded data on Tandem's t:connect® web application, improvements in glycemic control seen in the RCT were demonstrated in a diverse population with T1D (70). Studies done with Beta Bionics iLet (72) and Omnipod 5 (73) found a similar reduction in the time below range. These studies provide important data on the safety and efficacy of the Control-IQ HCL system but its utility, acceptability, and deliverability as an intervention to restore impaired awareness in a broad adult population with T1D needs investigation.

Table C.1: HCL planned for the study

Brand name of pump	CGM system	Carbohydrate Counting and Manual Bolus Delivery Required?	Tubing?	Infusion sets
Tandem Control IQ	Dexcom 6 or 7	Yes	Yes	Yes, various types
Beta Bionics iLet	Dexcom 6 or 7	No	Yes	Yes
mylife YpsoPump	Dexcom 6 or 7	Yes	Yes	Yes, various types
Omnipod 5	Dexcom 6 or 7	Yes	No	Included in pod
Medtronic 780g	Guardian 4	Yes	Yes	Yes, various types

As stated in section B, the primary outcome will be a composite of the rise in epinephrine and the rise in self-reported total symptom scores during experimental hypoglycemia compared to the initial scores measured at euglycemia. A response at 12 months will be assessed as positive (meaning restoration of hypoglycemia awareness) if the peak epinephrine response is 125 pg/ml greater than at baseline, and if the autonomic symptom scores are 20% greater than at baseline as has been demonstrated by Rickels et al (41). Rubin and colleagues also present data that demonstrates these endpoints are associated with restoration of the counterregulatory response (74).

D. Study Rationale

We will recruit individuals with T1D duration of at least ten years who display evidence of IAH (Gold score or Clarke score ≥ 4) (7, 8, 75). The main intention of our protocol during the first phase (0-12 months) of the study is to

investigate, in a randomized controlled trial, the ability of HCL to improve IAH. Our comparator is another active and effective education (UC + My HypoCOMPaSS), rather than the scientifically robust alternative of continuing UC alone, for two reasons, first that this enables us directly to compare the effect of HCL versus education (in the HCL naive group) and quantify the additive effect of education on HCL (in the HCL group), and second, because we believe it is more ethical (even when this includes CGM), to supplement the UC with My HypoCOMPaSS in this vulnerable patient group at high risk of severe hypoglycemia for 12 months. There are data from strong randomized controlled trials and real-world evidence supporting the impact of CGM with alarms in reducing the risk of severe hypoglycemia, and national guidance in the UK allows all people with IAH to access this therapy, which makes a non-active control arm unethical. A trial previously has evaluated suspend before low technology against pump therapy alone and found significant reductions in TBR and events of CGM hypoglycemia, as well as severe hypoglycemia, but no change in awareness (54). Furthermore, an adequately powered clinical trial evaluating HCL in restoring awareness of hypoglycemia in T1D has not been performed, thus justifying this approach. The second phase of the trial during months 12-24 will focus on HCL treatment "non-responders," i.e., those who do not show restoration of hypoglycemia symptoms and CRR during the clamp at 12 months, and on the durability of the intervention in maintaining hypoglycemia awareness response in those who demonstrated improvement on the month 12 clamp study.

Our trial design is structured to randomize those with previous experience of HCl either to continue HCl alone (receiving standard guidance to maximize time in range and minimize time in hypoglycemia) or also participating in the My HypoCOMPaSS educational intervention. The rationale is that it is possible that to improve impaired awareness, participants may need to remain on HCl for a longer period than 12 months. Thus, with this design we will be able to compare those who spend longer on HCl with the most up to date guidance vs those who receive an additional brief educational intervention designed to change their behavior in how they manage (and avoid) hypoglycemia.

Rationale for the HARPdoc arm of the trial during months 12-24: This intervention explores the hypothesis that a major contributor to persistent, treatment-resistant problematic hypoglycemia is related to cognitions, described by patients with IAH (61, 62, 76), that drive unhelpful behaviors that mitigate against successful hypoglycemia avoidance. Amiel and colleagues investigated the HARPdoc psycho-educational intervention addressing such cognitive barriers in a multi-center, randomized, parallel, two-arm trial in adults with T1D and treatment-resistant IAH (n=49 for HARPdoc and 50 for BGAT) and showed that, as well as reducing severe hypoglycemia and improving IAH scores, significantly reduced endorsement of unhelpful cognitions and as well as improving mental well-being (62). The HARPdoc trial cohort pre-dated HCL although participants had access to pumps and/or CGM, including some with automated insulin delivery features.

E. Inclusion and Exclusion Criteria

Inclusion Criteria:

- Ages 18-75 years
- Clinical diagnosis of type 1 diabetes
- Gold Score or Clarke Score ≥ 4 (highly associated with IAH) (7, 8, 75)
- Random non-fasting C-peptide < 200 pmol/L
- Diabetes duration ≥ 10 years
- A1c ≤ 10.5%
- Total Daily Insulin Dose of ≤ 1 unit/kg
- Ability to read and speak English (because validated non-English versions of the cognitive tests and the educational interventions are not available)

Exclusion Criteria:

- Medical conditions that limit participation in study activities, as determined by the PI (including but not limited to cognitive dysfunction, reduced hearing, reduced vision, cancer under active treatment, untreated angina, organ failure)
- Active alcohol or drug abuse. (As defined by DSM criteria of either 1) recurrent use of alcohol/drugs resulting in a failure to fulfill major role obligations at work, school, or home, 2) recurrent alcohol/drug use in situations in which it is physically hazardous, or 3) recurrent alcohol or drug-related legal problems)
- Social determinants of health that limit participation in study activities, as determined by the PI (including but not limited to homelessness, food insecurity, inadequate social support)
- Seizure disorder unrelated to hypoglycemia associated seizures, unless documented seizure-free for >12 months and on a stable regimen of anti-convulsant therapy
- Skin conditions that would preclude the use of a CGM
- Super-physiologic exposure to steroids within one month of enrollment
- eGFR < 45 mL/min/1.73 m^2
- History of bariatric surgery that irreversibly alters gut innervation and structure
- Hyper- or hypokalemia (serum potassium >5.5 or <3.5 mmol/L)*
- Hemoglobin < 10 g/dL*
- Medical condition that requires intermittent or continuous use of glucocorticoids at greater than physiological replacement doses
- Pregnancy, plan for pregnancy, or breast feeding
- Abnormal thyroid function tests of clinical significance, as determined by PI*
- Liver transaminases > 3 times the upper limit of normal*
- Hospitalization for mental illness in last year
- History of adrenalectomy

* At discretion of the PI, laboratory tests may be repeated once. If the participant is not eligible after the second attempt, then the participant. The participant may be screened again.

F. Participant Withdrawal

Participants can withdraw consent at any time. In addition, a participant may be withdrawn if conditions arise that will render the participant or caregiver unable to perform protocol related diabetes management tasks, as determined by the site principal investigator.

Participants who are withdrawn from the study will resume the medical treatment of their diabetes with a clinical care team of their choosing. The study personnel will transition the participant from their assigned intervention to a clinically relevant plan that can be managed by the future care team. Details about both the intervention and the transition plan will be shared in writing with the participant and his/her care team. Withdrawn participants will be asked to (1) undergo the clamp study and the pre-clamp study assessments before they withdraw to determine if the intervention impacted the study outcome, provided the clamp study is not a contraindication for their current health condition, and (2) provide access to basic clinical data, such as HbA1c and rate of severe hypoglycemia. After that clamp study, no further data collection will occur. The sample size calculation, described in Section P, accounts for withdrawn participants. All data collected prior to study withdrawal will be included in the study data base.

G. Recruitment Plans

Potential study participants will be identified mostly from clinical settings. Patients from ambulatory or hospital settings may be identified by diabetes care providers, including endocrinologists, diabetes educators, nutritionists, or other clinical staff caring for patients with diabetes. Patients also may be identified through electronic health records, databases, research networks, provider referrals, community events, study advertisements, and/or social media.

Advertisements will be displayed at the clinical centers and on their websites, on the main Consortium website for the study, at ClinicalTRials.gov, on social media, and through patient advocacy groups. In the United Kingdom, Patient Identification Centers (PIC) have proven to be useful in recruitment for clinical studies. Potential study participants may be approached using electronic communications such as email or patient portal, telephone, letter, or in-person to introduce the research study and review eligibility criteria. Potential participants will be approached about the study, with permission by their clinical care team. If local policy permits, potential participants may be directly contacted by a study team member or through institution-generated electronic communications or letters. The Consortium will form a Recruitment and Retention Committee to support the clinical centers in addressing challenges encountered with participant recruitment.

If local policy permits, potential study participants will be recruited while they are in clinical settings at the sites or at community events. If local policy permits, they may also be recruited via telephone or written communication.

Potential study participants will be recruited after they have had a clinical diagnosis of type 1 diabetes for at least ten years, which is typically the minimum disease duration required to develop an impaired CRR.

The screening process will occur after obtaining informed consent from a participant. If the potential participant contacts the research team to learn more about the project, the first contact will be by email, web site, phone, or text. At that time the potential participant will be contacted by phone for screening after obtaining a verbal consent to participate in the screening process. Alternatively, if local policy permits, the research team may reach out to a potential participant via telephone or email, with permission of the participant's provider, to inform them about the study. Once verbal consent is granted, the participant will be asked a series of questions as part of the screening process. If they meet the minimum inclusion criteria and do not possess any of the exclusion criteria (see Section E), then they will be scheduled for a face-to-face screening visit in the clinical research unit. The recruitment sites and their specific plans are briefly described below.

1. University of Leicester, University Hospitals of Leicester (United Kingdom)
   Leicester envisions most participants with Type 1 diabetes and problematic hypoglycemia will be currently seen within our clinical service. With appropriate local approvals, Leicester is able to run searches in its database to identify appropriate participants, who can then be approached at their next clinical appointment. Leicester uses a region wide electronic health records system called SystmOne that is shared system across primary and secondary care. With appropriate local approvals, Leicester also is able to run searches across the region for people with type 1 diabetes and impaired awareness of hypoglycemia. Leicester has a dedicated staff member from the local Clinical Research Network across the East Midlands. This region includes two other large clinical services in Derby and Nottingham, who each have over 5000 people with T1D (of whom at least 1000- 1500 would be expected to have IAH) and have over 300 patients on insulin pumps. Through its local research network, Leicester has a system to facilitate recruitment of participants to studies across the region. The Clinical Research Network also has a series of community events planned each year designed to increase recruitment from ethnic minorities into research. Leicester has a strong track record of recruitment into studies at Leicester. It was the third highest national recruiter to the NHS closed loop pilot, recruiting 51 participants in just under 3 months, and recruited to target within 8 weeks for the ADAPT closed loop study. Access to closed loop therapy through the NHS in this region is still comparatively, and so that may provide further incentive for participants in this area.

2. University of Kentucky
   Participant recruitment will be from the University's Health Care Network which includes 36 community clinics (including the Barnstable Brown Diabetes Center). A recent search indicates that the University of Kentucky's HealthCare System treats greater than 4000 patients with T1D who meet proposed age criteria for recruitment. Of note, the University of Kentucky has unique access to a pool of potential study participants from Eastern and Appalachian Kentucky, a region of lower socioeconomic status and many

known healthcare disparities. Informed written consent will be obtained. The population recruited will have racial and ethnic diversity and it is expected that the overall population recruited by the entire consortium reflect the demographic distribution of the U.S. population of individuals with T1D. All participants will be in good health as determined by medical history, physical examination, and fasting creatinine concentrations, hematocrits, and electrocardiograms that are within normal reference ranges.

3. University of Sheffield, Sheffield Teaching Hospitals
   All sites for the proposed clinical trial are University referral centers for T1D and hypoglycemia care. These centers form part of the United Kingdom Clinical Research Network (UKCRN) and have a common goal of providing the infrastructure to support high quality clinical research studies for the benefit of patients.

4. University of Melbourne
   The Diabetes Technology Research Group (DTRG) at the University of Melbourne (UM) has an excellent track record of meeting recruitment targets on time. To facilitate this end, UM has a database of over three hundred people with type 1 diabetes (T1D), with their demographic and clinical profiles documented, who have expressed an interest in participating in T1D technology related research. In addition, the T1D clinics at our affiliated teaching hospital (St. Vincent's Hospital Melbourne) comprise a database of over 700 people. Finally, Melbourne has a strategic agreement in place with Diabetes Victoria, the peak consumer body, in our state. A summary of studies conducted by the DTRG with descriptions of the protocols and major inclusion and exclusion criteria are published with their newsletter. In addition, the DTRG website has a list of all currently recruiting studies. Finally, Melbourne has a strong clinical team working across multiple clinical sites/hospitals with each site having similar access to participants, totaling a large population of people with T1D throughout the state. In addition to a strong track record with recruitment, UM also has <10% participant dropout from our technology studies at St Vincent's Hospital Melbourne involving over 300 participants. Typically, participants who engage in research regarding technologies for treating T1D are highly motivated to ensure the success of the trial and retention is generally good without the need for rigorous procedures to ensure retention. An important factor in determining retention in a study relates to participant selection and the provision of clear and unambiguous information regarding the requirements associated with the study. The DTRG has a protocolized consenting progress with a checklist to ensure that the consent of participants is conducted robustly. This includes information regarding the study, specifically emphasizing the duration of the study and the specific obligations of the participant. All participants will continue to be seen by their clinical team at frequencies as appropriate in line with usual clinical practice. The research team will ensure that the team responsible for the participants clinical care is informed of any matters pertaining to their health which may arise. All study visits will be scheduled in addition to routine visits and will be performed by the research team only. Finally, engagement of the study team includes regular check-ins to ensure that participants are safe and a 24-hour study helpline, both of which aids retention.

5. University of California San Diego (UCSD)
   UCSD has obtained IRB approval to search EPIC (electronic medical record system) for participants with T1D and key inclusion criteria and contact these participants via our electronic email system (UCSD MyChart). Searchable criteria include age 18-70, BMI 25-35, and A1c < 8.5%. There are currently 4,142 participants with T1D within the UCSD care system. Of these patients, **2,863 meet our search criteria**. Its IRB approval allows UCSD to reach out directly to these participants via MyChart with a message that describes the study, the research group, and how to directly contact the research group to enroll. UCSD has performed multiple clinical trials with the type 1 diabetes population and is fortunate to have a cohort of patients that return for subsequent trials. Having this cohort ensures that UCSD can quickly recruit reliable participants that are known by its group and have demonstrated an ability to follow protocol requirements. Additionally, the UCSD research group has recently created an Instagram, Facebook, and twitter account. It uses these social media platforms to promote awareness around its research. UCSD has also utilized these platforms to increase recruitment using IRB approved posts. Dr. Pettus, the Principal Investigator sees patients in a

dedicated T1D clinic which is another source of new participants for clinical trials. In addition, the endocrinology faculty members at UCSD are very willing to refer their patients to clinical trials. Dr. Pettus will notify providers of the study at grand rounds, fellows conferences, and with individual emails. This mechanism will assist in adding participants to the IAHC clinical trial. Dr. Pettus works with the non-profit group "Taking Control of Your Diabetes," which provides direct education to patients living with diabetes. This organization creates online/virtual content for education of patients with type 1 diabetes. The social media network via this organization obtains approximately 1.5 million views per month. UCSD has utilized this network previously to promote awareness regarding our research. All information regarding studies always includes IRB approved language.

6. AdventHealth
   Potential participants will be identified by EMR searches combined with manual chart reviews to exclude ineligible patients with exclusionary conditions. AdventHealth also will leverage its extensive experience with social media and local T1D advocacy groups (JDRF, ADA, Touched by Type One). Potentially eligible participants will be called by recruiting staff.

7. University of Pennsylvania
   The proposed study protocol will be registered on Clinicaltrials.gov and advertised through a Penn IRB-approved secure on-line system iConnect as well as the Consortium website. Outreach will be throughout the Penn Medicine system of diabetes providers and patients.

8. University of Minnesota
   More than 30,000 individuals with type 1 diabetes receive care in the M Health Fairview health care system affiliated with the University of Minnesota. This population has been the primary source of recruitment for research studies performed by Dr. Seaquist and her collaborators for the last 20 years. Participants are identified using the electronic medical record and then sent a letter by their physician that asks them to consider study participation. This letter is followed up with a phone call from a team member to provide additional information about the project and to learn if the potential participant meets inclusion criteria. Drs. Seaquist, Chow, and Moheet have also participated in the training of most endocrinologists in the greater Minneapolis/St. Paul area and maintain cordial relationships with these colleagues. Many of these endocrinologists support the recruitment efforts by posting study information in their clinics, sending their patients recruitment letters, and referring participants with type 1 diabetes and impaired awareness to the study group.

H. <u>Obtaining Informed Consent</u>

Informed consent will consist of a two-step process. The first step will be a verbal informed consent process for screening purposes (described in Section G), performed according to institutional guidelines to assess basic information. The second step of the informed consent will be the main study informed consent obtained via a face-to-face visit in the hospital or clinic or using a written informed consent process performed according to institutional regulatory board guidelines.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, as applicable. A consent form describing in detail the study procedures and risks will be reviewed with, and given to, the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her.

The consent form will include specific language that will clearly state participation in the study is voluntary and clarify that a decision not to participate will not alter the participant's relationship with the clinical center, its

doctors, and its medical staff, or the participant's quality of and access to care. This information will be reviewed with the participant and their family, if applicable.

Participants will be presented alternatives to participating and be informed that they can choose to withdraw at any time. Participants will be prompted and given time to ask any questions about the study and their participation, and the clinical center Principal Investigator or delegated study team member will answer the participant's questions. Participants will be given ample time to consider the decision to participate in the study before written consent form signature is obtained.

We will not recruit non-English-speaking participants because validated non-English versions of many of the cognitive tests and the educational interventions are not available. Individuals under the age of 18 years will not be enrolled.

I. Study Design

The CLEAR study invokes an adaptive design known as a sequential multiple assignment randomized trial (SMART) design, in which study participants will undergo two stages of randomization. Parallel studies will be conducted for patients who are either HCL naïve (Trial 1) or HCL non-naïve (Trial 2). Participants are randomized to interventions at the onset of the first stage (0-12 months), and are either kept on a successful treatment or re-randomized to alternative interventions at the onset of the second stage (12-24 months) if they are not responding to the initial interventions.

We will define HCL non-naïve participants as those who are using an HCL device at the time of study enrollment and have been on such a device for a minimum of 6 months. HCL naïve participants will be those who have never used a HCL device or who have not used a HCL device for the 12 months before study enrollment.

Figure I.1 below displays the stratified SMART design. The intervention comparison within the HCL naïve stratum (Trial 1) during the first stage is HCL versus usual care (UC) + My HypoCOMPaSS (MyHC), an IAH educational program. The intervention comparison within the HCL non-naïve stratum (Trial 2) during the first stage is HCL versus HCL + MyHC. The interventions at 12 months are detailed below:

HCL naïve stratum (Trial 1):

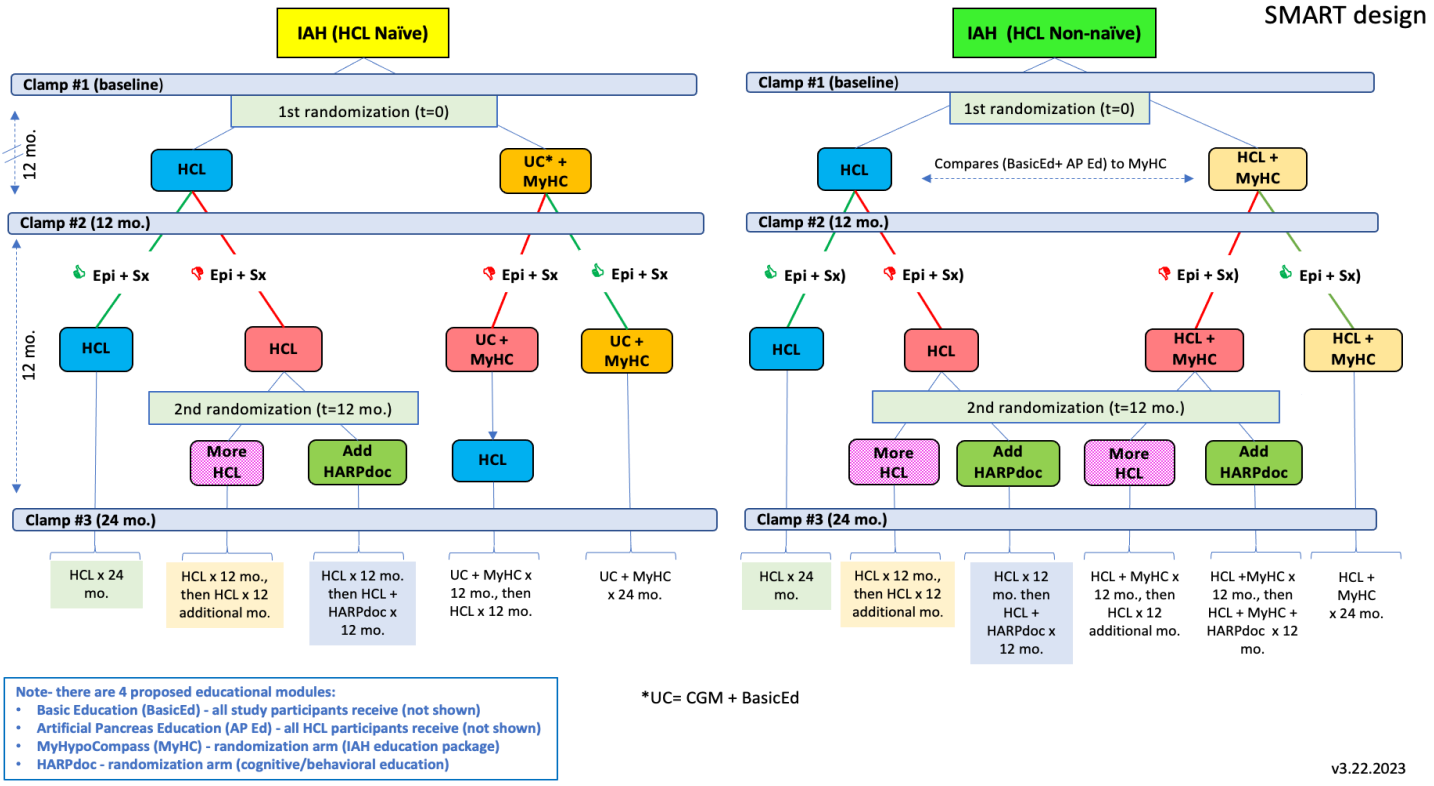
- Participants randomized to the HCL device who show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will continue with the HCL device for months 12-24.
- Participants randomized to the HCL device who do not show improved epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will be re-randomized to continued HCL (to determine if more time is needed for the intervention to be effective) or HCL + HARPdoc, an IAH psychoeducational program, for months 12-24.
- Participants randomized to UC + MyHC who show improved epinephrine and autonomic symptom responses as determined by the measurements at 12 months, will continue with UC + MyHC for months 12-24 to determine durability of improved epinephrine and autonomic symptom responses.
- Participants randomized to UC + MyHC who do not do not show restoration of the counterregulatory epinephrine and autonomic symptom responses as determined by the measurements at 12 months, will be assigned to HCL for months 12-24.

HCL non-naïve stratum (Trial 2):

- Participants randomized to the HCL device who show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will continue with the HCL device for months 12-24.

- Participants randomized to the HCL device who do not show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will be re-randomized to HCL alone (to determine if more time is needed for the intervention to be effective) or to HCL + HARPdoc, an IAH psychoeducational program, for months 12-24.
- Participants randomized to HCL + MyHC who show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will continue with HCL + MyHC for months 12-24
- Participants randomized to HCL + MyHC who do not show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will be re-randomized to continued HCL + MyHC (to determine if more time is needed for the intervention to be effective) or HCL + HARPdoc for months 12-24.

Figure I.1: Schematic of the stratified SMART study design for the CLEAR trial.



J. Study Visits and Procedures

Table J.1 below provides an overview of the study procedures during the course of the CLEAR trial, and more detailed descriptions appear after the table.

Table J.1: Study visits and procedures for the CLEAR trial

Visit Number	**2**	**3**	**4**	**5,6,7,8,9,10**	**11**	**12**	**13,14,15,16, 17,18**	**19**	**20**
Visit Name	Screening Visit	Pre-clamp 1	Clamp 1	Randomization **Year 1**	Pre-clamp 2	Clamp 2	Randomization **Year 2**	Pre-clamp 3	Clamp 3
Estimated time window	3 - 6wks before visit 3.	1 mo. before visit 4.	Month 0	Visit 5 = Randomization Visit 6 = +Mo. 1 Visit 7 = +Mo. 2 Visit 8 = + Mo. 3 Visit 9 = +Mo. 6 Visit 10 = +Mo. 9	1 mo. before visit 12	Month 11.5 – 12.5	Visit 13 = Mo. 0 / Randomization Visit 14 = +Mo 1 Visit 15 = +Mo. 2 Visit 16 = +Mo. 3 Visit 17= +Mo. 6 Visit 18 = +Mo. 9	1 mo. before visit 20	Month 24
In- Person Or Virtual	I	I	I	I or V	I	I	I or V	I	I
Enrollment consent	X								
Medical history & concomitant medication review	X				X			X	
Physical Exam	X				X			X	
EKG	X								
Cardiovascular assessment by history and physical	X	X			X			X	
Diabetes & Hypoglycemia Questionnaires	X				X			X	
Labs required for inclusion/ exclusion	X								
Blinded CGM instruction & application (for those not using Dexcom CGM)		X			X			X	
Activity monitor device application		X			X			X	
Explanation in how to use APPs		X			X			X	
Randomization				X			X		
Training on HCL device				X			X		
Instruction on intervention				X			X		
Introduction to surveys, questionnaires to be done during each clamp study		X			X			X	

Visit Number	**2**	**3**	**4**	**5,6,7,8,9,10**	**11**	**12**	**13,14,15,16, 17,18**	**19**	**20**
Visit Name	Screening Visit	Pre-clamp 1	Clamp 1	Randomization **Year 1**	Pre-clamp 2	Clamp 2	Randomization **Year 2**	Pre-clamp 3	Clamp 3
Estimated time window	3 - 6wks before visit 3.	1 mo. before visit 4.	Month 0	Visit 5 = Randomization Visit 6 = +Mo. 1 Visit 7 = +Mo. 2 Visit 8 = + Mo. 3 Visit 9 = +Mo. 6 Visit 10 = +Mo. 9 *above does not include time for Hypo-COMPASS education- see below.	1 mo. before visit 12	Month 11.5 – 12.5	Visit 13 = Mo. 0 / Randomization Visit 14 = +Mo 1 Visit 15 = +Mo. 2 Visit 16 = +Mo. 3 Visit 17= +Mo. 6 Visit 18 = +Mo. 9 *above does not include time for HARP-doc education- see below.	1 mo. before visit 20	Month 24
In- Person Or Virtual	I	I	I	I or V	I	I	I or V	I	I
Checklist to assess understanding of study topics	X								
Clamp Test (labs, surveys, telemetry monitoring)			X			X			X
Estimated time commitment	90 min	60-105 min	5-8 hours	~30-120 min depending upon intervention*	~60 min	5-8 hours	~30-120 min depending upon intervention*	60 min	5-8 hours

A more user-friendly version of Table J.1 for student participants, which appears in the informed consent, is as follows:

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Site or Phone Visit																				
What will happen at my visit?																				
Questions about health, disease, and medications																				
Physical exam																				
EKG																				
Labs/blood draw*																				
Questionnaire/App**																				
Devices																				
Education starts ***																				
Clamp Study (8-hour fast the night before)																				
Time needed	30-45 min.	90 min.	60-105 min.	5-8 hrs.	30 min.- 2 hrs.	30 min.	30 min.	30 min.	30 min.	30 min.	60-105 min.	5 - 8 hrs.	30 min.- 2 hrs.	30 min.	30 min.	30 min.	30 min.	30 min.	60-105 min.	5-8 hrs.

*1: Lab tests include: kidney, liver, pancreas, and thyroid function tests.

**2: The App used in this study will require a download to a personal smartphone.

***3: Mind-health education visits are scheduled separately. For participants randomized to receive these interventions, the additional time commitments are:

a. Year one HypoCOMPaSS- **5.5 hours** over 6 weeks, (one 2-hour workshop and 2 one-to-one visits of one hour).

b. Year two HARPdoc- a total of **34 hours** over six months (4 full-day workshops, in weeks 1,2,3 and 6; one-to-one visits of up to one hour in each of weeks 3 and 4, and two 2-hour group follow-ups at 3 and 6 months)

J.1. Visit 1 (initial screening visit)

The first contact with a potential participant (Visit 1) will likely be over email or the phone when the potential participant contacts the research team to learn more about the study. At that time the potential participant will be informed that they are being invited to join a study about regaining awareness of hypoglycemia using technology and education. Potential participants who express an interest will be provided an opportunity to consent to participate in the screening process verbally. Alternatively, if local policy permits, the research team may reach out to a potential participant with permission of the participant's provider to inform them about the study. Once verbal consent is granted, they will be asked a series of screening questions. If they meet the minimum inclusion criteria (age between 18-75, have the diagnosis of type 1 diabetes (Gold score or Clarke score ≥ 4), and have a diabetes duration of more than 10 years), then they will be scheduled for a face-to-face screening visit in the clinical research unit.

J.2. Visit 2 (screening visit)

The screening visit (Visit 2) will be in-person at the clinic or Clinical Research Unit (CRU). At this visit, the study informed consent discussion will take place prior to conducting study-related activities. A thorough medical history and review of all current concomitant medications will be obtained, and a physical exam will be done. The physical exam should include assessment of body systems as per local guidelines. Blood samples will be collected to evaluate that the participant meets the inclusion criteria for HbA1c and C-peptide, and that they do not have any of the laboratory exclusion criteria. An EKG will be done.

Trained study staff then will work through a checklist with the participant, with the purpose of identifying and addressing major knowledge gaps in topics related to the study. The purpose of the checklist is not to provide comprehensive diabetes education nor to replace the care participants should otherwise receive.

Completing the checklist should take 45 minutes or less. The total estimated time is actually 35 minutes with an additional 10 minutes to address major questions related to the Section topics.

Diabetes education materials from local resources can be provided as needed for participants to read in addition to the education provided during the session. If participants have questions beyond the scope of the checklist, besides providing materials, they should also be encouraged to seek further information from their regular diabetes educators or endocrinologists.

J.3. Visits 3, 11, and 19 (pre-clamp visits)

At the pre-clamp visits (Visits 3, 11, and 19), participants will be fitted with a Dexcom G6 Pro sensor (masked) that will be worn for approximately 28 days prior to the clamp procedure. An activity monitor will be provided to participants and they will be trained on its use. Additional data will be collected from participants during these ~28 days using the HypoMETRICS app to collect data on patient reported hypoglycemia, validated psychological and behavioral surveys, and physiological data collected from wearables and apps. The devices and the instructions for their use are described in Section M.1. Participants also will be given instructions for how to manage their diabetes on the night before the clamp study to ensure they have a blood sugar 70-180 mg/dl in the hours before the clamp, and avoid being below 54 mg/dl during the night.

J.4. Visits 4, 12, and 20 (clamp visits)

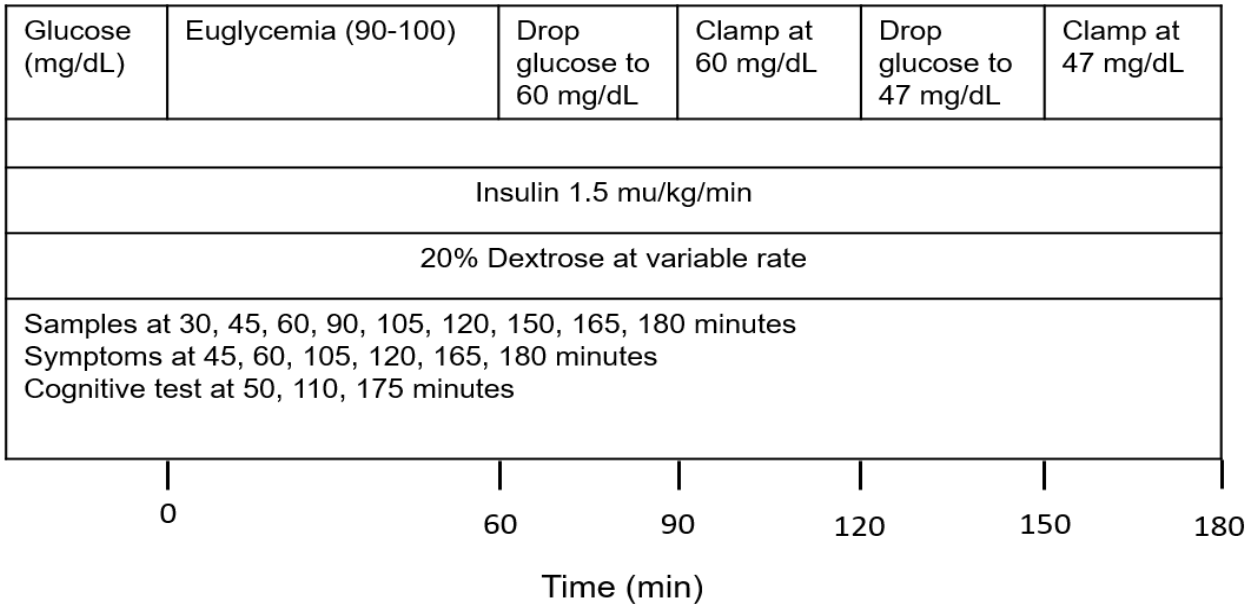
Participants will be admitted to the CRU in the morning in the fasting state (8 hours), or they may come to the CRU the night prior to the clamp study for the overnight fast. Participants will be instructed to target their sensor glucose to 90-150 mg/dl in the morning before the study begins. If AM capillary BG > 200 mg/dl or the CGM shows sensor glucose <54 for 15 consecutive minutes or more in the preceding 24 hours, the clamp study will be rescheduled. When participants arrive, the CGM and physiological data collected during the preceding 4

weeks will be available. The participant's CGM will be removed or silenced before study personnel assume control of blood glucose levels. Participants will be asked to practice the cognitive tests that will be done during the clamp. To prepare for the study, intravenous catheters will be placed in the forearms for the subsequent infusion of 1.5 mU/kg/min insulin, potassium phosphate or potassium chloride (4.8 mEq/hr [e.g., 100 mEq/L at 48 cc/hr or 120 mEq at 40 cc/hr]), and 20% dextrose as needed to maintain target glycemia and in a contralateral hand or forearm vein to collect blood samples.

Arterialized venous samples will be collected, preferably from a retrograde IV placed into a hand vein or the most distal site possible on the upper limb, using a heated box or heating pad throughout the procedure and analyzed using the glucose oxidase device that has been appropriately calibrated.

At the start of the clamp intravenous insulin infusion, the participant's insulin pump will be turned off. Intravenous insulin will be started at 1.5 mu/kg/min and plasma glucose, determined at bedside brought to 90-100 mg/dl and maintained there as needed with a variable rate infusion of D20W. If AM plasma glucose is 70-100 mg/dl, the dextrose infusion will be started at the same time as the insulin infusion in order to achieve the 90-100 mg/dl target. Baseline samples will be collected when BG = 90-100 mg/dl for 30 minutes, at t= 30, 45, and 60 min. Once participants have been clamped at 90-100 mg/dl for 60 minutes, the glucose will be allowed to drop to 60±2 mg over 30 minutes and then held there for another 30 minutes. At that point the glucose will be dropped to 47±2 mg/dl over 30 min and held for 30 more minutes before the blood sugar is returned to normal. If the blood glucose does not drop to 60 mg/dl by minute 85, the investigator may increase the insulin infusion rate to 2.0 mU/kg/min so the target glucose can be reached. Figure J.4.1 illustrates the clamp protocol.

Figure J.4.1: Clamp protocol



During the clamp study, participants' EKG will be monitored via cardiac monitoring. Samples for glucose will be collected every 5 minutes for immediate analysis using a YSI or Analox machine. Samples for later measurement of catecholamines (epinephrine and norepinephrine), glucagon, pancreatic polypeptide, FFA, free insulin, and glucose will be obtained at baseline and minutes 30, 45, 60, 90, 105 120, 150, 165, 180 in the order stated here (Figure J.4.1). During the clamp steps at euglycemic at 60 mg/dl and at 47 mg/dl, participants will be asked to complete a number of assessments in standard order using a tablet or laptop device. First, hypoglycemia-associated symptoms will be assessed using the Towler questionnaire (5). Then participants will be asked to estimate their heart rate for a brief undisclosed period of time by paying attention to bodily feelings, such as those associated with the action of their heart. Participants will be instructed not to take their own pulse (a measure of interoception). Next, they will be asked to do the 4-choice reaction time test where they are

presented repeatedly with four stimuli and asked to decide which of four responses is correct (e.g., when a circle is in the third box on a screen, the participant presses the number three). They will then be asked to do the Trail-Making B test that requires individuals to connect dots that are filled with sequential numbers (1,2,3…) and letters of the alphabet (a,b,c, …) randomly placed on a page/screen. The task is to connect each letter to the number that is equivalent in sequence, e.g. A with 1, B with 2, etc. in a timed format. Hypoglycemia-associated symptoms will be asked again at each level (90 – 100 mg/dL, ~60 mg/dL, and ~47 mg/dL).

After the last step is completed, IV insulin and potassium will be stopped and IV and/or oral glucose, including a meal, will be provided to restore euglycemia. Blood or plasma glucose will be checked every 15-30 minutes and adjustments will be made in the rate of D20W infusion to keep blood or plasma glucose at 90-100. Once the subject has achieved a blood or plasma glucose ≥ 90, the glucose infusion should be tapered and until ultimately discontinued. If the blood or plasma glucose is >80 at the next check after the glucose infusion is discontinued, this should be confirmed once more at least by blood glucose prior to discharging the subject.

Table J.4.1: Assessments during the clamp procedure

Assessment #1	Assessment #2	Assessment #3	Assessment #4
Towler Questionnaire (5)	Interoception	4-choice Reaction Time Test	Trail-Making B Test

The Biostatistics Research Center (BRC) will house a Central Lab, at which the biochemical analyses will be performed.

J.5. Visits 5 and 13 (randomization visits)

Each of the two randomizations will be done at a visit in 1-5 days after the clamp study. For the initial randomization assignment, most participants will be instructed how to implement their assigned intervention in a face to face meeting with study personnel in the CRU, but participants randomized to remain on their existing insulin delivery system or MDI may be seen virtually.

First randomization assignment intervention will be for months 0-12. Second randomization assignment intervention will be for months 12-24. During the intervention periods, participants will be seen in person (or virtually) every one month for the first three months and then at six and nine months after randomization. At each visit, modifications to the treatment regimen will be made as necessary to minimize time below 70 mg/dl to <1% while maximizing time in range 70-180 mg/dl. based on the CGM and insulin delivery / dose data shared with study staff. Participants will be asked to quantify how many episodes of severe hypoglycemia that they've had since the prior contact/visit. Participants also will be instructed to contact study staff about diabetes management in between visits if necessary. The time spent in these interactions will be collected to control for any confounding at the end of the study.

At the second randomization visit, which will occur after the 12-month clamp and data collection, participants will be seen virtually or may return to the CRU to learn of their next intervention assignment. As noted in Figure I.1, participants who experience improved CRR and autonomic symptom responses during their second clamp will remain on their originally assigned intervention. Those who do not show improvement of counter-regulatory epinephrine or autonomic symptom responses will be assigned to the intervention as shown in Figure I.1. Participants new to the HCL intervention may require an in-person visit for instruction on how to implement their intervention. They then will be seen virtually monthly, and in the CRU every 3 months, for 12 months.

K. Educational Interventions

The CLEAR trial includes two educational interventions, My HypoCOMPaSS and HARPdoc©.

My HypoCOMPaSS (MyHC) is a brief, standardized psycho-educational program delivered in small groups. Facilitated discussions focus on advocating rigorous avoidance of hypoglycemia while maintaining time in target glycemic range. The four compass points (NESW) are used to illustrate the imperatives: 'Now; No delay' (never delay hypoglycemia treatment); 'Establish your Extra risks' (and times when risk is highest); 'Scan for Subtle Symptoms' (of hypoglycemia); be Wary even While asleep (through watchful detection and active prevention of hypoglycemia while asleep).

The program was designed following experience in the pilot study (77), and informed by insights from a qualitative study, which identified the cognitive, behavioral and psychological barriers to preventing severe hypoglycemia (78). Evidence for the program is derived from the MyHC RCT, in which adults with long-standing type 1 diabetes and impaired awareness of hypoglycemia experienced improved awareness of hypoglycemia, decreased biochemical hypoglycemia (time below <3mmol/L), and prevention of recurrent severe episodes, without increasing HbA1c (34). These benefits were observed across all arms, regardless of technology allocation (34), and sustained at two years (57). Furthermore, HbA1c improved from 24 weeks to 24 months (-0.5%; -5mmol/mol), while the initial reduction in fear of hypoglycemia was sustained. Subsequent analysis has shown that participation in the program was associated with a reduction in the attitudinal barrier 'hyperglycemia avoidance prioritized' from baseline to 24 weeks and maintained at 24 months (57). Incomplete prevention of subsequent severe hypoglycemia was associated with persistence of the cognition 'asymptomatic hypoglycemia normalized' (14).

Participants will take part in the brief My HypoCOMPaSS workshops (approximately 2-3 hours) in small groups (four to six people), via remote videoconferencing. During the workshop, they will complete the My HypoCOMPaSS workbook, guided via discussion and activities by a facilitator. Facilitators (specialist fellows or nurses) will be trained in the My HypoCOMPaSS principles and facilitation skills by the team at the University of Newcastle (UK), using a structured curriculum, guided by the My HypoCOMPaSS facilitator handbook. To minimize the possibility of contamination between arms, the workshops will be delivered either by a study team member not involved in the insulin adjustment intervention or if unavailable at a clinical site, centrally by a facilitator within the same country.

The HARPdoc© intervention is a psychological intervention, delivered to small groups of adults with T1D (n = approx. 6) by two diabetes educators trained and supported by a clinical psychologist, which uniquely addresses the unhelpful health beliefs of people with treatment resistant IAH and SH (27, 79). The educators use motivational interviewing and cognitive behavioral theory to address the main cognitive barriers to hypoglycemia avoidance addressed above. In an RCT, in people whose problematic hypoglycemia had persisted (at high rates) despite use of structured education in flexible insulin therapy and availability of pumps and CGM, HARPdoc successfully reduced severe hypoglycemia, as did its comparator, Blood Glucose Awareness Training or BGAT, a psycho-educational intervention lacking the cognitive elements, and likewise restored awareness (61). HARPdoc however also improved mental health, reducing scores for diabetes distress, anxiety and depression (61). Further preliminary evidence also shows improved quality of life. We propose to use HARPdoc as a rescue therapy for people who fail to regain awareness of hypoglycemia after the first 12 months of participation in our trial, randomizing such "non-responders" to receive either HARPdoc or longer use of their existing allocated therapy including HCL.

The program is curriculum-driven and delivered over six weeks. There are four full-day group sessions (weeks 1, 2, 3, and 6) and two one-to-one sessions lasting up to an hour (weeks 4 and 5). Family members are invited to day 6. All sessions are delivered in an on-line platform such as Microsoft Teams. The educators de-brief with a clinical psychologist funded via the Sheffield center for up to one hour after each of the full days. There is a 2-hour group follow-up at months 3 and 6.

People failing to regain awareness of hypoglycemia at the assessment at 12 months will be randomized to receive either HARPdoc or continue their allocated therapy including HCL. HARPdoc will be delivered on an on-line platform, so that participants do not need to attend at the center. We will train educators from our centers prior to starting HARPdoc courses. Each course requires two educators, and we propose to create two or three US training centers

and one each in Australia and UK due to issues of timing. Because HARPdoc happens after My HypoCOMPaSS is completed in the trial, My HypoCOMPaSS educators also can deliver HARPdoc. We will provide an on-line training course for the educators. With permission from the participants and educators, sessions will be audio-recorded for later assessment of validity.

L. Questionnaires

The Towler Questionnaire (5) will be administered during the clamp procedures at 0, 12, and 24 months. All of the remaining questionnaires will be administered via the Database Management System (DMS) maintained by the Biostatistics Research Center. Table L.1 lists the schedule of all the questionnaires.

Table L.1: Schedule of questionnaires

Questionnaire	Visit	2			
	# Items	Pre-screen	0-7 days before clamp 1 (visit 4)	0-7 days before clamp 2 (visit 12)	0-7 days before clamp 3 (visit 20)
Gold Score (7)	1	X	X	X	X
Clarke Score (8)	8	X	X	X	X
DAFNE UK Score (9)	1		X	X	X
HypoA-Q Score – 5-item Impaired Awareness subscale plus 15 remaining items (10)	5 (+ 15)		X	X	X
Hypo-METRICS (item 27 – hypoglycemia event or prevention) (11)	1		X	X	X
Multidimensional Assessment of Interoceptive Awareness (MAIA-2) (80)	37		X		
20-item Toronto Alexithymia Scale (TAS-20) (81)	20		X		
Adult ADHD Self-Report Scale (82)	6		X		
Big Three Perfectionism Scale – Long Form (83)	16		X		
Hypo-METRICS (11)			X	X	X
Hypoglycemic Confidence Scale (12)	9		X	X	X
Hypoglycemic Fear Survey – II (HFS-II) (13)	33		X	X	X
Attitudes to Awareness of Hypoglycaemia (A2A) Scale (14)	19		X	X	X

Questionnaire	**Visit**	**2**			
	# Items	**Pre-screen**	**0-7 days before clamp 1 (visit 4)**	**0-7 days before clamp 2 (visit 12)**	**0-7 days before clamp 3 (visit 20)**
Type 1 Diabetes Distress Scale (T1-DDS) (15)	28		X	X	X
Diabetes Self-Management Questionnaire (16)			X	X	X
Diabetes Management Experiences Questionnaire (DME-Q) (17)	23		X	X	X
PROMIS Sleep Disturbance – Short Form 8a (18)	8		X	X	X
Hospital Anxiety and Depression Scale (19)	14		X	X	X
12-Item Hypoglycemia Impact Profile (HIP12) (20)	12		X	X	X
EQ-5D-5L (21)	5		X	X	X
Open-ended questions inviting free-text response	2-3		X	X	X

M. Devices

The CLEAR trial will include the use of continuous glucose monitors, hybrid closed loop pumps, the Hypo-METRICS app via personal cellular phones, and wearable activity monitors.

M.1. Continuous Glucose Monitor (CGM)

A Continuous Glucose Monitor (CGM) is an FDA-approved device that can be used in patients with diabetes to measure glucose levels continuously throughout the day and night. CGM systems take glucose measurements at regular intervals, 24 hours a day, and display the readings as dynamic real-time glucose data with direction and rates of change. They also have alerts and alarms that can inform the individual of high or low glucose readings. CGM helps patients to proactively manage high or low glucose levels, and also provides insight into the impact of meals, exercise, or illness on glucose levels over time. CGM can also improve diabetes management by helping to minimize the guesswork that comes with making treatment decisions based on single glucose readings from a glucometer. Studies have shown that CGM systems help reduce A1C levels (84, 85) and reduce the risk for hypoglycemia, whether users are on insulin injections or pump therapy (86).

Study participants will select the CGM system to use based what will work with their HCL device or, for those on usual care, personal preference. At the time of this writing, the Dexcom G6 or G7, Libre Freestyle 2, and Medtronic Guardian 4 are the CGMS that work with available HCL. All of these work in a similar manner. Systems are factory-calibrated and accurate enough (MARD ~ 9%) to not require regular fingerstick glucose tests to calibrate the system, having a non-adjunctive designation from the FDA. Sensors can be worn for 10-14 days

depending on the model. CGM systems have three components: a sensor, a transmitter, and a display device (receiver and/or compatible smart device). The sensor is a small device with a tiny sensor wire, the width of a human hair, that is inserted just under the skin using a disposable automatic applicator. An adhesive patch holds the CGM in place, so the sensor can continuously measure glucose levels in the interstitial fluid providing a reading and calculated rate of change every five minutes. A small reusable transmitter attaches to the sensor and sends real-time CGM readings wirelessly to a receiver using Bluetooth technology. The receiver, or a compatible smart device such as smartphone, smart watch, or tablet, displays real-time glucose data, sends custom alerts and notifications when certain glucose thresholds, set by the health care team, or by the user with their advice, are reached, when glucose is rising or falling rapidly, and warns the user of impending hyperglycemia or hypoglycemia. Using proprietary applications may be available on both iOS and Android platforms, glucose data and alarms can be shared with up to ten family members or friends approved by the user, which enhances an in-built hypoglycemia prevention feature.

Adapted from Dexcom Inc.

The CGM systems we plan to use in this study are widely used across the world and are generally considered safe and well-tolerated. No major risks are expected with the use of the CGM devices. Pain and bleeding with insertion is minimal. Skin irritation can occur in those sensitive to adhesives.

The CGM systems we plan to use in this study are FDA-approved for making treatment decisions. They are convenient and easy to use, helps reduce the burden of frequent fingerstick testing, and improves diabetes management. Patients can gain valuable insight into their glucose levels, rate and direction of change in glucose, and how to proactively manage their diabetes.

M.2. Hybrid Closed Loop (HCL)

There are five hybrid closed loop systems that could be used by the CLEAR participants:

- Tandem T slim x2™ with Control iQ algorithm
- Omnipod® OP5 with Smartcontrol
- YpsoPump with CamAPS algorithm
- Beta Bionics iLet Bionic Pancreas
- Medtronic 780g

In observational studies, they all deliver similar glucose control and low time below range. There are slight differences in the algorithms, and we will control for system use in our analyses.

M.3. Hypo-METRICS app

The Hypo-METRICS app, deployed on the uMotif platform, will be used to conduct ecological momentary assessments (EMA) to analyze the events of patient reported hypoglycemia (87). Participants will be shown how

to download the app and how to use it to collect data about hypoglycemia and how it may affect them. This app was developed and validated as part of the HypoRESOLVE project (88).

Each morning the participants will receive a notification on their phone that will take them to a brief check-in. This will ask some questions about how they feel, and ask if they have had any episodes of patient-reported hypoglycemia events since the last check-in. Patient-reported events are defined as events where the participant experienced typical symptoms of hypoglycemia that resolved with carbohydrate ingestion, or if they had been alerted to hypoglycemia or impending hypoglycemia by an alert or had a measured glucose (on CGM or CBG) below 70 mg/dl).

The app also will ask participants to report the symptoms and intensity of symptoms they experienced for each of their patient-reported hypoglycemia events. These data will provide a granular understanding of symptoms people experienced.

M.4. Wearable Activity Monitor

A smartwatch will be used to monitor physiological parameters including heart rate variability, sleep, and physical activity in study participants. Patients will be provided the wearable monitor and will receive training on proper use of the device from a member of the study team in the clinic or remotely (through tele-health). Upon completion of the training, participants will be asked to download the app (free) on their mobile phone to allow data uploading. Participants will wear the watch on their wrist for 28 days before their in-patient visit for the clamp procedure (baseline, 12 months, and 24 months). The smartwatch will be worn continuously on the wrist, including at night, to determine the heart rate and sleep parameters throughout the day.

Data will be downloaded using the device app. Deidentification of data will follow the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations. The data captured from the wearable activity monitors, such as wear time, step count, sleep metrics, and heart rate, will be integrated with CGM data to allow analysis of hypoglycemia relative to heart rate variability, physical activity, and sleep.

N. Insulin Protocol

Study participants will provide their own insulin during the study unless they are financially unable to do so. In that case, the study will provide the insulin. Lyspro or aspart insulin or their more rapid acting analogs will be used in the pumps according to manufacturer's recommendations. Participants on multiple daily injections (MDI) will continue their prescribed basal and rapid acting insulin analog preparations. Participants will provide their own supply of extended-life glucagon as rescue therapy. The number of times glucagon is administered will be monitored.

A strict protocol for insulin adjustment will be followed. The glycemic goals for all CLEAR participants are as follows:

- minimize time with hypoglycemia to achieve time below 70 mg/dL (3.9 mmol/L) less than 1% and time below 54 mg/dL (3.0 mmol/L) to be 0%
- maximize time in the normal glucose range of 70-180 mg/dL (3.9 mmol/L – 10 mmol/L)

Upon enrollment into the study and after administration of the basic education checklist and baseline measurements of glycemic control are obtained (initial CGM download), the following initial interventions will be implemented:

- If using CSII or HCL review sensor glucose metrics, daily sensor glucose profiles, average daily insulin requirement and proportions of basal and bolus insulin over the previous 14 days will be collected
- If using MDI review sensor glucose metrics, daily sensor glucose profiles, and average daily long-acting insulin dose and rapid-acting insulin dose and proportions over the previous 14 days will be collected

- For HCL naïve participants randomized to HCL consider a 14 – 28-day glycemic stabilization period prior to HCL initiation per investigator discretion (Can be used for insulin delivery adjustment or pump training on SAP), see Appendix 1 for suggested initial pump settings
- If participants are not meeting the study-defined goals for sensor glucose TBR (< 70 mg/dl) < 1% and TIR (70 – 180 mg/dl) maximized, or have experienced a clinically important, serious episode of hypoglycemia (sensor glucose < 54 mg/dl for 15 min or blood glucose < 54 mg/dl), adjustments to insulin delivery settings will be considered prioritizing avoidance of hypoglycemia
- All participants will undergo basic education and sensor setting review at the initial visit as described in Sensor settings and education below

With respect to follow-up visits:

- If using CSII or HCL review sensor glucose metrics, daily sensor glucose profiles, average daily insulin requirement and proportions of basal and bolus insulin over the previous 14 days will be collected
- If using MDI review sensor glucose metrics, daily sensor glucose profiles, and average daily long-acting insulin dose and rapid-acting insulin dose and proportions over the previous 14 days will be collected
- If participants are not meeting the study-defined goals for sensor glucose TBR (< 70 mg/dl) < 1% and TIR (70 – 180 mg/dl) maximized, or have experienced a clinically important, serious episode of hypoglycemia (sensor glucose < 54 mg/dl for 15 min or blood glucose < 54 mg/dl), adjustments to insulin delivery settings will be considered prioritizing avoidance of hypoglycemia
- Review sensor settings and basic education as detailed in Sensor settings and education below if required per investigator assessment

With respect to sensor settings, the principle is to use "actionable" alarms based on best evidence for hypoglycemia avoidance and minimizing TBR <70mg/dl (3.9 mmol/l):

- High alarm will be set to 250 or 300 mg/dl [13.9 or 16.7 mmol/l] per investigator discretion. For those with HbA1c > 8%, an initial high alarm at 300 mg/dl (16.7 mmol/l) should be considered for the first few weeks
- High snooze will be set to 2 hours
- Rate of rise alert will be turned OFF
- Predictive high alerts will be turned OFF
- Low alert will be set to 70, 75 or 80 mg/dl [3.9, 4.2 or 4.4 mmol/l] per investigator discretion in order to balance achievement of hypoglycemia avoidance with an individual's perceived alarm burden
- Predictive low alert will be turned ON and set to 30 minutes
- Rate of fall alert may be turned ON at a rate of > 2 or 3 mg/dl/min [> 0.111 or 0.220 mmol/l/min; 2 or 3 arrows]

With respect to sensor education:

- Study team will ensure the participant is aware of best practice according to the sensor manufacturer on sensor insertion, initialization, use and calibration
- Study team will perform a skin assessment where sensors will be worn, review issues encountered with CGM use and provide education as needed
- Participants may calibrate sensor periodically (every few days and as needed) at times when sensor glucose is stable (horizontal arrow)
- Participants will be encouraged to turn off "auto-updates" on their phones to minimize any issues caused by phone operating system updates
- Study team will check the participant knows how to pair the sensor with their pump (when applicable) and how to review or share the sensor data via phone apps
- Study team will provide education on when to perform finger-stick blood glucose checks:
    - If sensor reading is over 300 mg/dl (16.6 mmol/l) for more than 2 hours [check blood glucose and ketones]
    - If sensor reading remains < 70 mg/dl (3.9 mmol/l) > 15 minutes after hypoglycemia treatment

- If sensor reading is < 54 mg/dl (3.0 mmol/l)
- If in the opinion of the participant, the sensor reading does not match what they expect it to be
- If the participant feels a discrepancy exists between the finger stick blood glucose and sensor glucose, they should do a calibration with a finger stick blood glucose checked again once glucose is stable (horizontal arrow)

With respect to hypoglycemia prevention and treatment:

- If predicted low or falling > 2 or 3 mg/dL/min [> 0.111 or 0.220 mmol/l/min; 2 or 3 arrows] and within the normal glucose range [70 – 180 mg/dL (3.9 – 10.0 mmol/L)], take 4-8 grams of fast-acting carbohydrate (e.g., glucose tablets)
- For low alert take 8-12 grams of fast-acting carbohydrate
- If Urgent Low alarm sounds [54 mg/dL; 3.0 mmol/L] take 12-16 grams of fast-acting carbohydrate
- Additional 8-12 grams of fast-acting carbohydrate may be required after 15 – 20 min of initial treatment if sensor glucose is not stable or rising and fingerstick blood glucose confirms on-going hypoglycemia (<70 mg/dL)

With respect to pump education (if applicable):

- The study team will ensure the participant is able to safely use the pump including:
  - Confirm and document pump and sensors parameters
  - Meal and correction bolus procedures
  - How to change reservoirs, cannulas, and infusion sets
  - How to turn on closed loop
  - Participant and care partner will be assessed on how to respond to safety/alert notifications
  - How to operate the pump in “non-HCL” mode when necessary.
- Study participants will be advised to enter accurate information into and use the bolus calculator for all boluses
- Participants will be advised to administer all mealtime boluses 15 minutes prior to eating
- Participants will be required to use insulin recommended by the manufacturer and to change reservoirs and infusion sets every 2-3 days
- How to recognize infusion site failure → if sensor glucose is > 250 mg/dl [13.9 mmol/l] for over 3 hours or > 300 mg/dl [16.6 mmol/l] for over 2 hours and the trend is not falling despite giving a correction bolus, assume infusion site failure and follow sick day rules (see Figure N.1 for further details)

With respect to nutrition education:

- Study Participants should be aware of common foods that contain carbohydrates
- For those who are not skilled in carbohydrate counting, they will be provided local on-line resources for carbohydrate counting and will be encouraged to use the 15-45-60 rule:
  - For small snacks – 15 grams
  - For medium sized meals – 45 grams
  - For main meals with large portions of carbohydrate - 60 grams
- Study advised to bolus 15 minutes pre-meal wherever possible:
  - If not sure how big the meal is - to bolus for 30 grams upfront and then bolus for the remainder as they are eating
  - If they forget to bolus for a meal, and are within 60 minutes of starting the meal, they can bolus for ½ the carbohydrate content consumed
  - If they forget to bolus and > 60 minutes since starting the meal, do not administer prandial bolus and use a correction bolus based on current glucose

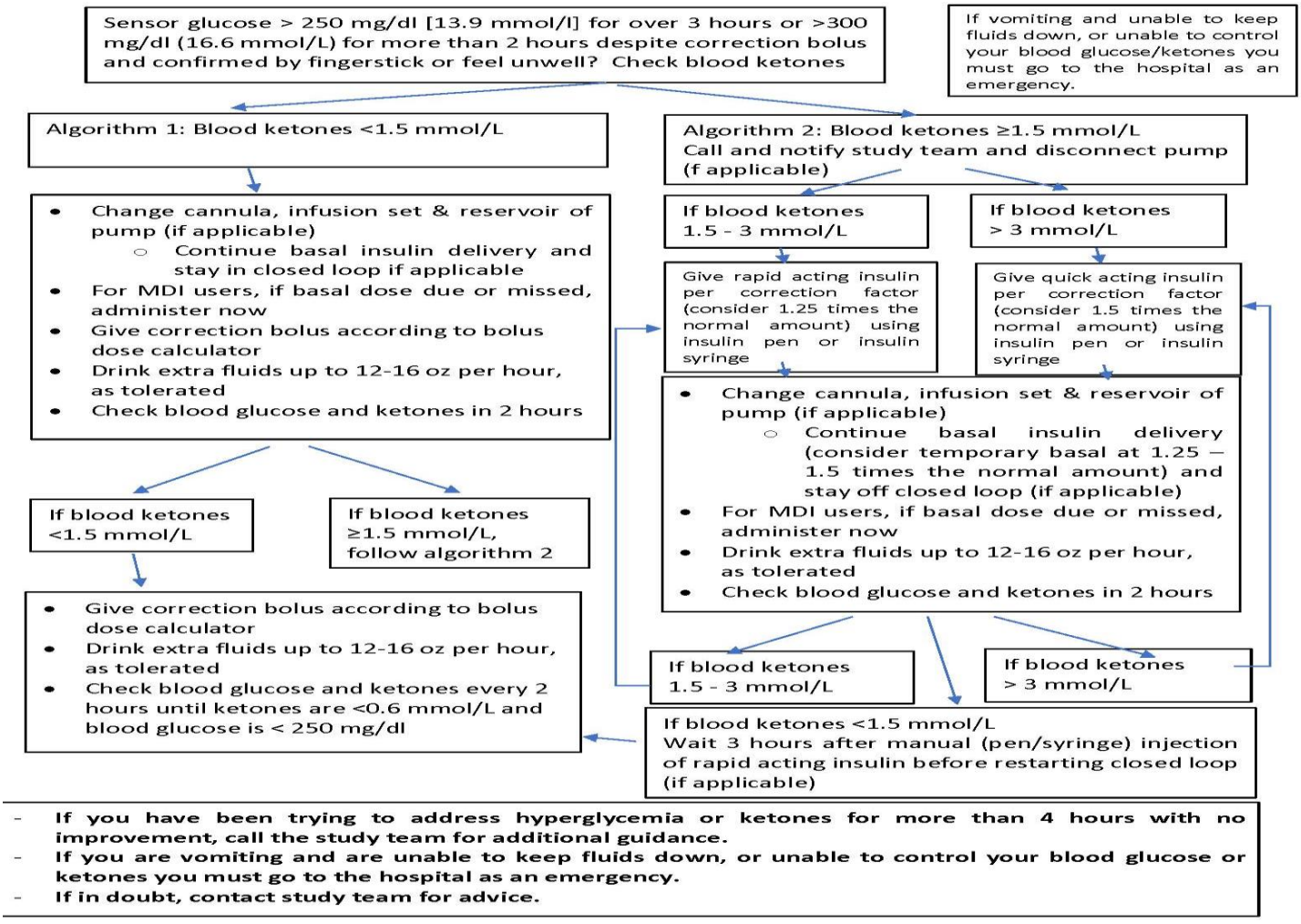
With respect to exercise education, the following protocol relates to moderate to intense exercise lasting > 30 minutes – changes may not be necessary for shorter exercise that is < 30 minutes in duration:

- Set the exercise target (for HCL users) or basal rate reduction (for standard pump users) up to 2 hours pre-exercise whenever possible, whereas MDI users may consider reducing the dose of basal insulin by 20% prior to anticipated prolonged activity
- Do NOT preload with carbohydrates but consider an ~ 15-gram carbohydrate snack if glucose is < 100 mg/dl and pump is already in exercise mode (for HCL users) or has a basal reduction in place (for standard pump users) within 15 minutes of exercise start
- Consider consuming 4-8 grams of fast-acting carbohydrate every 15 minutes for the duration of the exercise
- Consider taking 50% of the required bolus (i.e. reducing the carbohydrate content entered into the pump by 50%) if planning to exercise within 2 hours of a meal

Suggested insulin pump settings for HCL initiation:

- Review TDD over the last 14 days on the pump or MDI (for MDI users, consider a 20% reduction in TDD)
- Basal rate: calculate total daily basal as [total daily dose (TDD) of insulin ÷ 2] and then program a "flat-basal" rate as the total daily basal ÷ 24, for example, if TDD = 48 units, then basal rate = [48 ÷ 2] ÷ 24 = 1.0 units/hr
- Insulin to Carbohydrate Ratio: will be set as 350/TDD for the whole day, for example, if TDD = 48 units, the Insulin to Carbohydrate Ratio = 350/48 = 1:7 grams carbohydrate
- Insulin Sensitivity factor: will be set at 2100/TDD mg/dl [120/TDD mmol/L], for example, if TDD = 48 units, the Insulin Sensitivity factor = 2100/48 = 44 mg/dl or 120/48 = 2.5 mmol/L

Figure N.1: Unexplained hyperglycemia and sick day rules



O. Randomization

The Biostatistics Research Center (BRC) will randomly assign participants to their interventions, as indicated in Figure I.1, via its web-based data management system (DMS). Randomization will be stratified according to clinical center and T1D duration (< 25 years and ≥ 25 years). After a research coordinator confirms that a participant at day 0 is eligible for enrollment, the participant completes the baseline hyperinsulinemic-hypoglycemic clamp (see Section J.4), the research coordinator will enter the private and secure DMS via the internet and enter the appropriate information. The research coordinator then will receive the intervention assignment that the participant will follow for the first 12 months. After the 12-month visit with the second clamp, and after the lab analysis of epinephrine is determined, the research coordinator again will enter the DMS and enter the appropriate information and receive instructions as to whether the participant will maintain the current intervention or be re-randomized to a new intervention as indicated in Figure I.1. Study interventions will not be blinded.

P. Sample Size

The target enrollment for the Consortium is 324 participants (184 in the HCL-naïve stratum for Trial 1 and 140 in the HCL non-naïve stratum for Trial 2). We allow for a maximum of 15% withdrawal at the 12-month follow-up visit, so we anticipate at least 272 participants completing the 12-month follow-up visit.

We will use a randomized trial (SMART) design, in which study participants will undergo two stages of randomization. Participants are randomized to interventions at the onset of the first stage, and are re-randomized to alternative interventions at the onset of the second stage (after 12 months of follow-up) if they are not responding well to the initial interventions. In addition, we stratify the design based on whether participants currently do not use hybrid closed loop devices (HCL naïve stratum) or do use such devices (HCL non-naïve stratum), as well as stratify according to clinical center and T1D duration (< 25 years and ≥ 25 years).

The intervention comparison within the HCL naïve stratum during the first stage is HCL versus usual care (UC) + My HypoCOMPaSS (MyHC), an IAH educational program. The intervention comparison within the HCL non-naïve stratum during the first stage is HCL versus HCL + MyHC.

For Aims 1-2, we base the sample size calculation on the assessment performed at the end of the first stage (months 0-12 post-randomization). A sample size of 184 participants in the HCL naïve stratum (Trial 1) yields 90% statistical power with a two-sided, 0.05 significant level test for comparing HCL (50% success rate) versus UC + MyHC (76% success rate) (3), i.e., detecting a difference of 26%, while allowing for a 15% withdrawal rate. Although this study was based on the Gold score and not on CRR, there is a strong correlation between the two measures. Furthermore, a sub-study of the HypoCOMPASS Trial has been published reporting a marked increase in catecholamines (as measured by metanephrine) in 18 participants who had received the HypoCOMPASS intervention (58). A sample size of 140 participants in the HCL non-naïve stratum (Trial 2) yields 90% statistical power with a two-sided, 0.05 significant level test for comparing HCL (20% success rate) versus HCL + MyHC (50% success rate), i.e., detecting a difference of 30%, while allowing for a 15% withdrawal rate. Table P.1 displays the effect sizes that can be detected with 80% and 85% statistical power as well.

Table P.1: Effect sizes for different levels of statistical power.

Power	HCL Naïve HCL vs UC + MyHC (N = 184)	HCL Non-naïve HCL vs HCL + MyHC (N = 140)
80%	53% vs 76%	23% vs 50%
85%	52% vs 76%	22% vs 50%
90%	50% vs 76%	20% vs 50%

With respect to Aims 3-4, the statistical power for comparisons is diminished because of the splintering into numerous subgroups. For example,

- within the HCL naïve stratum, the maximum statistical power for comparing two subgroups is 54%
- within the HCL non-naïve stratum, the maximum statistical power for comparing two subgroups is 60%

Q. Analysis Plan

Q.1 Statistical analysis

We will invoke the intent-to-treat (ITT) principle for all primary statistical analyses, i.e., we will analyze the data according to the randomized and assigned interventions and include all available data. We also will perform secondary statistical analyses that involve a per-protocol approach in which participants are required to

- use of the HCL in "closed loop/auto mode" at least 75% of the time
- attend at least 50% of the assigned education sessions
- undergo, at a minimum, the clamp procedure at baseline and at 12 months
- agree to the verbal consent for screening and sign the written informed consent for the study
- not display any breach of data confidentiality

As indicated above, we will stratify the SMART study design according to current HCL use (HCL naïve stratum for Trial 1 and HCL non-naïve stratum for Trial 2). We also will include clinical center and T1D duration (< 25 years and ≥ 25 years) as stratifying variables. The primary outcome measured at the 12-month follow-up visit is whether a study participant, based on hypoglycemic awareness (Towler Questionnaire increase ≥ 20% over baseline clamp response) and counter-regulatory response (CRR) (epinephrine increase ≥ 125 pg/ml over baseline clamp response) during a clamped hypoglycemia procedure, can continue on the current intervention or requires re-randomization or assignment to an alternative intervention. Thus, the primary outcome variable is binary, so we will compare the first-stage interventions at the 12-month follow-up visit, separately within the HCL naïve and the HCL non-naïve strata, via binary regression models. We will incorporate a complementary log-log link function for the binary regression models because it yields estimates of the relative risk, whereas a logistic link function yields estimates of the odds ratio. Relative risks are preferred because the study is a prospective, randomized clinical trial. We first will perform an unadjusted analysis of the primary outcome variable at the 12-month visit in which we only adjust for clinical center and T1D duration. Next, we will perform an analysis in which we adjust for the additional regressors of age, sex/gender, race/ethnicity, social determinants of health, current insulin dose, and c-peptide.

Analysis of the primary outcome at the 24-month visit is more complex because there are five distinct intervention arms within the HCL naïve stratum (Trial 1) and six intervention arms within the HCL non-naïve stratum (Trial 2). However, as noted in Section I, three of the intervention arms are common across the HCL naïve and HCL non-naive strata:

- HCL x 24 months
- HCL x 12 months, then HCL x 12 months
- HCL x 12 months, then HCL + HARPdoc x 12 months

First, we will compare the 24-month outcome to the 12-month outcome within each arm that maintains the same intervention during the 24-month duration. We will not impose any multiple comparison adjustments for these 24-month versus 12-month comparisons within each arm.

Next, we will perform pairwise comparisons of the intervention arms with respect to the primary outcome variable (binary) within each stratum. For convenience, we assign labels to the 11 intervention arms at 24 months:

- Intervention A (HCL naïve): HCL × 24 months
- Intervention B (HCL naïve): HCL × 12 months, then HCL x 12 additional months
- Intervention C (HCL naïve): HCL x 12 months, then HCL + HARPdoc x 12 months
- Intervention D (HCL naïve): UC + MyHC x 12 months, then HCL x 12 months

- Intervention E (HCL naïve): UC + MyHC x 24 months
- Intervention F (HCL non-naïve): HCL x 24 months
- Intervention G (HCL non-naïve): HCL x 12 months, then HCL x 12 additional months
- Intervention H (HCL non-naïve): HCL x 12 months, then HCL + HARPdoc x 12 months
- Intervention I (HCL non-naïve): HCL + MyHC x 12 months, then HCL x 12 additional months
- Intervention J (HCL non-naïve): HCL + MyHC x 12 months, then HCL + MyHC + HARPdoc x 12 months
- Intervention K (HCL non-naïve): HCL + MyHC x 24 months

Because of the anticipated small sample sizes for these 24-month intervention arms, the statistical power will be compromised for each pairwise comparison. Nevertheless, we will impose multiple comparison adjustments (Hochberg step-down procedure) within each of the following sets of intervention comparisons:

1. Intervention A vs. Intervention B vs. Intervention C
2. Intervention D vs. Intervention E
3. Intervention F vs. Intervention G vs. Intervention H
4. Intervention I vs. Intervention J vs. Intervention K

For the three intervention arms that are common across the two strata, we can enhance the statistical power via a meta-analysis that pools the results of the pairwise comparisons across the HCL naïve and HCL non-naïve strata (89):

Interventions A and F vs. Interventions B and G vs. Interventions C and H

The first set of important secondary outcomes includes CRR hormone/metabolite responses to experimental hypoglycemia during the clamp study (glucagon, pancreatic polypeptide, free fatty acids, and glucose infusion rate). These CRR hormone/metabolic responses will be measured at baseline, 12 months, and 24 months, so we will apply longitudinal data analyses via linear mixed-effects models. Another important set of secondary outcomes includes continuous glucose monitor (CGM) metrics, such as time below range (<70 and <54 mg/dl), time in range (70-180 mg/dl), time above range (>180 and >250 mg/dl), coefficient of variation (CV = sensor glucose SD/mean), low blood glucose index (LBGI), high blood glucose index (HBGI) and events of serious, clinically important episodes of hypoglycemia defined as at least 15 min with sensor glucose <54 mg/dl . The CGM metrics also will be measured at baseline, 12 months, and 24 months, so we will apply longitudinal data analyses. For the time below range, the time in range, and the time above range, we also will examine separately during periods of sleep and awake and apply a beta regression model embedded within a generalized linear mixed-effects model (90). We will apply more in-depth analyses of the CGM data via the R package CGManalyzer (91).

For the number of severe hypoglycemic events, we will apply a zero-inflated negative binomial regression embedded within a generalized linear mixed-effects model and include the logarithm of the duration as an offset variable (90). All of these longitudinal data models will include

- fixed effects for the interventions and the regressors defined above for the analysis of the primary outcome variable
- random effects for the study participants

We will construct adjusted means and adjusted intensity rates, along with their confidence intervals, as descriptive statistics from the estimated models. We will investigate moderating effects of the regressors on the interventions via interaction terms.

We will derive additional secondary outcomes from (a) wearable activity monitors, and (b) physical examinations and medical histories. We will apply longitudinal data analyses for these outcomes in a manner similar to the analysis plans for the CRR hormone/metabolite responses and the CGM metrics. In addition, we will investigate the effect of pre-clamp variables (physiological variables, co-morbidities, lifestyle factors) on the epinephrine and symptom response.

Another set of secondary outcomes include the variables from self-reported on-line questionnaires listed in Table L.1 that are administered post-randomization. We will apply linear and generalized linear mixed-effects models to account for the repeated measurements while comparing the randomized groups during the course of the 24-month follow-up period, in a manner similar to that described above for the primary outcome.

For all of the analyses of the secondary outcomes, we will perform the 12-month comparisons and then perform the 24-month comparisons via the multiple comparison adjustments as described above for the primary outcome. The number of secondary outcomes is extremely large, which increases the risk of Type 1 error inflation, so we will report unadjusted p-values and adjusted p-vales via the false discovery rate (92).

The statistical analyses described above are based on likelihood, restricted likelihood, and pseudo-likelihood approaches, which yield valid results when the data are missing at random (MAR). Therefore, we will not perform any data imputation for the initial analyses of the primary and secondary outcomes. This should work well, unless the withdrawal rate prior to the 12-month clamp procedure exceeds the anticipated 15%. However, we will perform sensitivity analyses via controlled multiple imputation to investigate the possibility of there being data that are missing not at-random (MNAR) (93, 94).

We will perform a variety of subgroup analyses with the primary and secondary outcomes, such as sex/gender, race/ethnicity, T1D duration (< 25 years and ≥ 25 years), and baseline HbA1c (< 8% and ≥ 8% [64mmol/mol]).

We will not perform any interim analyses for efficacy because we have invoked a SMART design in which we will evaluate the efficacy response of every study participant at 12 months. If a participant's efficacy response is not satisfactory, then we will randomize or assign that participant to another intervention.

Q.2 Qualitative Analysis

Qualitative data from the open-ended questions collected online will be imported into NVivo (or similar software) and analyzed using reflexive thematic analysis (95). The research methods will be similar to the Hypo-RESOLVE qualitative study methods (95). A coding framework will be developed, and two researchers will independently code the data: one researcher coding all responses, and the other researcher coding a random selection of at least 20% of responses allowing for assessment of coder agreement. Semantically related codes will then be clustered to develop overall themes. Themes will be reviewed, iteratively developed and discussed with the wider co-author team. Depending on data quality, completion rates, and technical feasibility, the reflexive thematic analyses may be replaced by or used in combination with machine learning driven approaches, for example topic modelling, which may be more suitable for theme development in extensive qualitative datasets (96).

R. Data Management and Data Security

We will use the Data Management System (DMS) developed by the Penn State Department of Public Health Sciences for study data collection and management, including participant enrollment, data entry, data validation, queries, data corrections, participant tracking and sample tracking. The DMS is a secure, web-based application. It is designed to be direct data entry so most data will be entered directly into the DMS in real-time. Data may be collected on paper in back-up circumstances, and in those situations, the Clinical Centers will be asked to enter data according to guidelines provided in the Manuals of Procedures and secure such data in accordance with their institution's policies.

Limited identifiers will be associated with each participant's study ID. Only those identifiers that are required will be collected and they will be encrypted before storage in the DMS database. Clinical Centers are instructed to not send patient identifiers through email. In the event that email is needed, secure email will be used. Any correspondence received at the BRC is reviewed and identifiers are redacted per a standard operating procedure.

S. Data and Safety Monitoring Plan

S.1. Adverse Events and Serious Adverse Events

Data will be reviewed on a monthly basis with the IAHC Steering Committee. The IAHC BRC will provide data reports to the Steering Committee at each meeting (currently twice per month). The NIDDK will appoint a Data and Safety Monitoring Board (DSMB) that will review study progress, safety of study participants, and progress of enrollment on a biannual basis.

We will document and report all serious adverse events (SAEs) that occur. We will classify SAEs as expected or unexpected, and related or unrelated to study protocol, as defined below.

Definitions

Serious adverse event (SAE): Any new medical condition or worsening of a known medical condition that results in death, hospitalization, emergency department visit, persistent or significant disability that occurs within 48 hours that are above minimal risk.

Expected adverse event: Any event that is described in the risks section of the protocol (protocol Section 10.0) or informed consent that is a known risk of one of the study interventions and/or procedures.

Unexpected adverse event: Any event that is not a known risk of one of the study interventions and/or procedures, as described in the protocol (protocol Section 10.0) or informed consent document.

Related adverse event: Any adverse event that is classified as possibly, probably, or definitely related to the study procedures by the site Principal Investigator.

Unrelated adverse event: An adverse event that is classified as not related to the study interventions and/or procedures by the site Principal Investigator.

The BRC also will accumulate and summarize non-serious adverse events (AEs) that occur. The BRC will prepare summaries of AEs and SAEs for review to ensure participant safety and identify trends. The BRC also will provide summaries of accrual, retention, and adherence to allow for monitoring of study progress and data integrity.

For events that meet the SAE specified in Section S.1, the Clinical Center Principal Investigator, or responsible study staff, will enter an SAE form with available information within the following timelines:

- All deaths and immediately life-threatening events will be submitted within 24 hours of site awareness
- SAEs, other than death and immediately life-threatening events, will be submitted within 3 business days of site awareness

The BRC will notify the Principal Investigators, the sIRB, the NIDDK Project Scientist and Program Officials, and the DSMB. Additional required information and source documentation will be entered and uploaded to the DMS as soon as available. Study-defined SAEs will be followed until resolution or stabilization. Clinical Centers will notify the BRC of Reportable New Information as defined by the sIRB (described in more detail in the Manual of Procedures) within six business days of site awareness, and the BRC will report such information to the sIRB according to Penn State IRB policy. The BRC will track all protocol deviations and violations; however, only deviations and violations meeting criteria for Reportable New Information (RNI), as defined by the Penn State sIRB, will be reported to the sIRB.

We will collect safety information during study visits and phone visits, as well as any time the participant contacts the clinic outside a scheduled visit to report an event. We will collect the data via CRFs, which the clinical centers will enter into the study database and will include event description, event dates, severity, relatedness, outcome, and treatment. The CLEAR participant visit schedule over the 24-month period appears

in Table J.1. Clinical centers will contact study participants on a regular basis between study visits. Clinical centers will instruct participants to notify the clinic promptly should an SAE occur. Clinical center coordinators will inform the Principal Investigators as soon as SAEs occur and proceed with gathering necessary information (including event description, event dates, treatment, outcome, etc.) and any source documentation. Required CRFs will be entered, and source documentation uploaded to the study database within the timelines, and appropriate individuals notified, as described below.

S.2. Data and Safety Monitoring Board (DSMB)

In addition to the responsibility of the Principal Investigators for oversight, study monitoring will be performed by (1) an independent DSMB assembled by the NIDDK and composed of members with expertise in appropriate clinical, statistical, and scientific disciplines, and (2) the sIRB. The DSMB will meet bi-annually to assess safety, study progress and data integrity for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of an NIDDK-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the NIDDK. Bi-annual DSMB meeting minutes, documenting their review of the safety data, accrual data and data integrity, will be forwarded to the sIRB for review.

The BRC will report to the DSMB descriptive statistics of AEs and SAEs for each intervention arm and perform formal statistical tests as requested by the DSMB. If the DSMB does request formal statistical tests, then we will construct Fisher's exact tests to compare intervention arms with respect to AE/SAE occurrence and Jonckheere-Terpstra trend tests to compare intervention arms with respect to AE/SAE severity. The DSMB may decide that the Steering Committee should be privy only to the descriptive statistics that are aggregated across all intervention arms. If so, then the BRC will comply with that reporting requirement.

The DSMB may recommend to the NIDDK the suspension or premature termination of this clinical trial if there is sufficient reasonable cause. The Principal Investigators are responsible for promptly notifying all parties and providing the reason(s) for the termination or suspension. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Data that are not sufficiently complete and/or evaluable
- Any other issue that cannot be addressed, and causes the DSMB and/or NIDDK to recommend study closure

S.3. Site Monitoring

Remote site visits will be conducted regularly and on-site visits will be conducted, as necessary. Remote monitoring is highly efficient for reviewing source documents. These documents can be scanned and uploaded into the secure departmental DMS for review and verification. The data on these documents are compared to the data entered into the consortium's database.

Clinical site monitoring is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. The BRC will perform monitoring for this study remotely, with on-site monitoring to take place on an as-needed basis. The BRC will evaluate study processes and documentation based on the International Council for Harmonization (ICH), E6: Good Clinical Practice guidelines (GCP). Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) contained within the Manuals of Procedures. The CMP will specify the central and remote monitoring activities (e.g., informed consent review), as well as the on-site monitoring activities to be performed if

determined to be necessary. During both remote and on-site monitoring, participant confidentiality will be maintained and PHI protected. Staff from the BRC will conduct monitoring activities and, when applicable, provide reports of the findings and associated action items in accordance with the details described in the CMP. The BRC will provide documentation of monitoring activities and findings to the site study team, the study Principal Investigators, and the NIDDK Program staff. The BRC will ensure that study investigators resolve in a timely manner any issues, problems, or need for corrections that arise during the conduct of the study. The NIDDK reserves the right to conduct independent clinical site monitoring as necessary.

The BRC will maintain protocol-specific reports on data quality. The QC report summarizes the number of missed study visits, data entry, total data queries sent and performance in terms of timely query resolution. All metrics are abstracted directly from the DMS. The BRC Scientific Coordinator will work the BRC Data Manager to assign protocol violations, protocol deviations, and protocol exceptions as warranted during study implementation. These errors and exceptions will be summarized in the protocol violation report. Each Clinical Center will have access only to its site's report via the secure website.

The BRC will program data validation error checks into the DMS that will be executed real-time to alert the user during data entry to values that violate the database constraints defined for each variable or identify discrepancies between values within the same data collection form or across data collection forms within the same defined time point. The Clinical Center can address the errors found after entering each form or view/print an entry error report after completing data entry for a packet of related forms. They can return to the Participant Data module later to fix the entry errors. When some values are identified as errors but are confirmed correct, the Clinical Center can mark the error(s) as "unresolvable," and explain why the value(s) is (are) correct. The "unresolvable" comments will be regularly reviewed by the BRC to identify errors that should not have been designated as "unresolvable." The Clinical Center will be required to upload any source documents associated with each data collection form into the Participant Data module for review at the BRC. More complex data validation error checks will be executed nightly to identify illogical data or data discrepancies across different types of data collection forms, time points, or other biological sample tracking or specimen repository data. The Error Tracking module communicates with the Clinical Center in resolving data errors identified via data error checks or remote monitoring. Entry errors not resolved by the Clinical Center (during or post data entry) and more complex errors identified by the BRC through nightly batch processing of data will automatically populate into the module for resolution by the data manager.

S.4. Clinical Trial Monitoring

The Department of Public Health Sciences at the Penn State College of Medicine maintains a team of Clinical Trial Monitors who will provide clinical trial monitoring services to the BRC. Clinical trial monitoring is a risk-based quality control process for evaluating the research team's adherence to Good Clinical Practice (GCP), the study protocol, and any applicable sponsor or federal regulations. During the monitoring sessions, DPHS will verify the presence of all essential and regulatory documents, review the participant informed consents, perform source document verification of data stored in the electronic database, confirm participant eligibility, ensure the protocol has been implemented as planned, verify that all protocol deviations/violations are recorded, review items related to participant safety (planned clinical and laboratory assessments, adverse events and concomitant mediations), verify all serious adverse events were reported to the appropriate individuals in the specified time period, review the receipt, dispensation, and tracking of the investigational product (if applicable), and ensure that all data errors and data queries have been resolved. The Clinical Trial Monitors will submit a report to the principal investigator following each monitoring session. Reports also will be forwarded to the single IRB, the local IRBs and the Research Quality Assurance offices.

T. Participant Risks

T.1. Hyperinsulinemic-Hypoglycemic Clamps

The lowest level we will bring the blood glucose down to is 45 mg/dL. Such blood glucose levels are routinely experienced in the ambulatory setting by our trial population (T1D with IAH). During the hyperinsulinemic-hypoglycemic clamp, investigators will have precise control of blood glucose levels which is a safety feature that is not possible in the ambulatory setting in people with T1D on a day-to-day basis. Extremely low blood sugars (<40 mg/dL) will be avoided. The hypoglycemia nadir (47±2 mg/dL) will be achieved in three gradual steps (90-100, 60±2 and 47±2 mg/dL) and participants will in total experience <60 minutes of level 2 hypoglycemia (<54 mg/dL). Some participants may experience symptoms from experimental hypoglycemia that will be assessed by the investigative team. The magnitude of symptoms participants will develop depends on the integrity of their hormonal responses to hypoglycemia. We anticipate under hypoglycemic conditions in our study, participants will to variable degrees feel anxious, shaky, hungry, sweaty and be more aware of their heartbeat. Some participants may develop a headache and others may have no symptoms at all. Obtaining intravenous access for insulin and dextrose infusion during hypoglycemic clamps may cause bruising or mild inflammation, which may be uncomfortable, but usually resolves in a few days. To obtain arterialized-venous blood for measurements during hypoglycemic clamp studies, we will place the non-dominant hand or arm in a warming chamber or heating pad for the duration of the clamp. The participant's hand or arm will feel warm, but should a heating box be used, the temperature will be set no greater than 55˚C (for reference, a moderately warm shower or bath is usually set at 43˚C).

The main risk associated with hypoglycemic clamps is the potential for arrhythmias during clamps; however, the protocol has been performed in thousands of participants in previous studies and arrhythmias have been very rarely reported (97). To put these results in context, in one of the global sites, these procedures have previously been performed over 500 times on healthy volunteers and those with diabetes, including T1D, and there have been no reported major adverse events. The clamp protocol in the proposed study has been created by the investigators in the IAHC, many of whom are recognized as world experts in the performance of this methodology based on a large number of publications. In order to minimize the risk of arrhythmias, we will exclude participants with active ischemic heart disease or cardiac arrhythmias, or serious intercurrent illness. There will be continuous electrocardiographic (EKG) monitoring throughout the hyperinsulinemic-hypoglycemic clamp along with regular heart rate and blood pressure monitoring and potassium supplementation. A trained health care professional will be present in all clamps and resuscitation facilities, including magnesium, will be available. Should the participant experience any serious adverse effects from the hypoglycemic clamp, insulin will be stopped immediately, and blood glucose rapidly brought to the normal range with intravenous dextrose within minutes. A qualified member of the research team will be contactable should participants experience any adverse effects during the study period. Arrangements will be made for admission to hospital should the participant be unfit to go home. Emergency admission facilities are located on or near the same site where hyperinsulinemic-hypoglycemic clamps will be performed. If any clinically significant abnormalities are found on investigations performed as part of this study, we will inform the participants' primary care physician or hospital diabetes team for further management as necessary.

Effects of hypoglycemia on the brain: The brain uses glucose as an obligate fuel and experimental hypoglycemia down to 45 mg/dL affects cognitive function (98). This resolves completely when blood sugars are brought back to normal. It is important to highlight that at the level of hypoglycemia we will induce, participants will remain fully conscious and able to communicate freely throughout the hypoglycemia period. This means that if they feel unwell and would like us to stop the study, they will be able to instruct us to stop at all times and we can bring their glucose levels up to normal levels rapidly. We do not expect any long-lasting harmful effects of the limited experimental hypoglycemia as proposed in this study.

T.2. Venipuncture

Obtaining venous blood throughout the study may cause mild bruising or inflammation which is self-limiting. We will monitor venipuncture sites throughout the study and especially after clamp visits. The amount of blood we

will obtain throughout the study (300 mL during each of the three visits with the clamp procedure, spaced 12 months apart) will not cause anemia. However, we will assess safety bloods at screening.

T.3. Sub-Cutaneous Catheters in Insulin Pump and CGM

There is a low risk of developing a skin reaction where the CGM sensor insulin infusion needle is inserted. Participants with a known allergic reaction to medical grade adhesives will be excluded. We will also regularly monitor these sites for signs of infection, inflammation and retention of foreign bodies during catheter change which have been rarely reported with use of this technology.

T.4. Hypoglycemia

One risk in our study is that of hypoglycemia given our trial population of adults with T1D and IAH. Rates of hypoglycemia are expected to decrease with trial interventions as hypothesized but generally study hypoglycemia frequency will not be higher than what the participant experiences in their day-to-day self-management of T1D. As CGM may not always reflect current glycemia, participants will be asked to always corroborate CGM sensor glucose values with finger stick capillary blood glucose measurements if they feel hypoglycemia and/or the CGM value is not as expected.

T.5. Hyperglycemia

Hyperglycemia and eventually ketonemia can occur if insulin delivery is interrupted. This may occur with insulin pump failure and/or if the CGM sensor is significantly under-reporting hyperglycemia. Participants will be asked to keep an in-date long-acting basal analogue insulin for subcutaneous injection throughout the study in cases of prolonged pump issues/failure to avert Diabetic Ketoacidosis (DKA). As for hypoglycemia, participants will be asked to corroborate CGM readings with capillary blood glucose if they are symptomatic of hyperglycemia or if the CGM readout is not as expected.

T.6. Questionnaires

We will ask participants to fill out psychological and social outcomes exploring their beliefs and attitudes towards their diabetes and hypoglycemia. In addition, we will change usual diabetes treatment for 50% of participants who are naïve to Hybrid Closed Loop and assess cognitive function during experimental hypoglycemia in those undergoing hyperinsulinemic-hypoglycemic clamps. Some participants may find aspects of this mildly distressing and these interventions may induce feelings of anxiety. Our past experience from studies that have used similar questionnaires suggests this will be uncommon. Further, assessment of diabetes distress, awareness status and some other measures are part of routine clinical care and therefore participants may have encountered similar questionnaires before. It will be emphasized that participants can choose not to answer specific questions and there will be support available from the study team.

T.7. Wearable Activity Monitors

There are no risks associated with wearing the smartwatch, however, the case is made of fiber-reinforced polymer and the strap is made of silicone. These may be irritating to the skin for some participants.

U. Protections Against Risks and Potential Benefits

U.1. Informed Consent

Recruitment will be conducted in 8 global sites (five in the US, 2 in the UK and one in Australia). The study will undergo research ethics committee IRB (and Research Ethics Committees in the UK and Australia) and UK Health

Regulatory Authority (HRA) approval as is standard practice in the UK. Any amendment to the protocol, including the consent form, will require REC/IRB approval before changes are implemented. All consent procedures will comply IRB/REC regulatory requirements and adhere to principles set out in Good Clinical Practice (GCP) and the Declaration of Helsinki. Written, informed consent, using the final version of the approved designated consent form for this study, will be obtained prior to any study procedures being carried out. Minors (<18 years of age) and those judged to be without the mental capacity to provide informed consent will not be enrolled into the study. All study procedures, interventions, risks and potential benefits will be explained by a medically qualified member of the research team, listed on the delegation log. Participants will have the chance to read the informed consent form/participant information sheet for as long as they need, and will be able to ask any questions, prior to signing. Participants will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Samples collected up to the point of withdrawal will only be used after withdrawal if the participant consents for this, otherwise they will be destroyed. However, data collected up to that point will be used for analysis, and this will be explicitly stated in the participant information sheet and consent form. One copy of the consent form will be given to participants, one copy kept in the investigator site file and one copy placed in participants medical records.

U.2. Hyperinsulinemic-Hypoglycemic Clamps

We will mitigate the risks associated with these studies through the following strategies:

- Excluding those participants with comorbidities (see Exclusion Criteria in Section E) or receiving concomitant medication likely to significantly increase the risk of taking part in the study specifically with respect to induction of experimental hypoglycemia
- Performing hyperinsulinemic-hypoglycemic clamps with an experienced multi-disciplinary team with ample past experience of safely conducting similar studies with rigorous assessment and monitoring protocols
- Performing hyperinsulinemic-hypoglycemic clamps in a dedicated Clinical Research Center with access to 24-hour emergency medical and critical care cover
- Performing hyperinsulinemic-hypoglycemic clamps under continuous EKG monitoring, with frequent measurement of vital signs and extremely close monitoring of blood glucose levels during the clamp using a state-of-the-art near patient glucose analyzer.

U.3. CGMs, HCLs, and Activity Monitors

We will mitigate risks associated with trial technology with the following strategies:

- Performing a skills assessment at enrollment to ensure participants are equipped with fundamental principles to facilitate safe self-management of T1D using flexible intensive insulin therapy. Any skill gaps will be addressed before participants can progress in the trial
- Providing bespoke training in trial technology to trial participants depending on their level of familiarity with trial devices and coinciding with use of devices in the study periods
- The trial design visit schedules and visit frequency are designed to ensure any emerging issues with technology can be anticipated and where system issues occur these can be expeditiously resolved
- Outside of scheduled study contact, clinical sites will set up a dedicated telephone assistance line and email address to allow participants to obtain timely support within the next business day, in addition to a standard operating procedure for investigators to troubleshoot issues with each trial device and minimize risk of hypoglycemia and hyperglycemia
- CGM use throughout the study will be unblinded for ethical reasons. Participants will therefore be able to adjust low and high glucose and predictive and rate of change alerts and alarms. Participants will be instructed to set the low glucose alarm not lower than 70 mg/dL. The exception occurs when a participant uses a non-Dexcom CGM of uses finger sticks during the month prior to a clamp visit – such

an individual in this situation will be provided a blinded CGM.

- The Dexcom G6 CGM has a fail-safe low glucose alert at <54 mg/dL which cannot be manually overridden. Participants will be instructed to corroborate all low glucose alerts with capillary blood glucose measurements and treat confirmed hypoglycemia with initially quick (15 grams) acting carbohydrates and then longer-acting carbohydrates and reassess glucose values. Participants will be asked to set the CGM high glucose alarm not higher than 300 mg/dL or a level more clinically appropriate for the participant, based on the judgment of the PI. Participants will be instructed to corroborate high glucose alarms with capillary blood glucose values. To treat hyperglycemia, participants will be instructed to administer insulin as per their insulin correction factor and reassess glucose values. If hyperglycemia persists (values >300 mg/dL > 2 hours), participants will be instructed to take additional insulin, ensure pump insulin infusion circuit is intact with no occlusions and contact the study team for additional advice and if needed a clinical assessment.
- Use of an HCL system by participants builds in protection against hypoglycemia and hyperglycemia. For example, the Control-IQ algorithm issues a predictive hypoglycemia alert if a sensor glucose of <70 mg/dL is anticipated within the following 15 minutes. The hypoglycemia alert consists of a message on the system display and a vibration alarm which is repeated and persists if not acknowledged by the user. Participants will be instructed to respond to these prompts by ingesting carbohydrate to prevent hypoglycemia and by checking capillary blood glucose and treating hypoglycemia with carbohydrates if detected. The Control-IQ algorithm will automatically increase insulin delivery in response to hyperglycemia but will issue a predictive hyperglycemia alert if a sensor glucose of >200 mg/dL is detected and is not anticipated to fall within the following 30 minutes. The hypoglycemia alert consists of a message on the system display and a vibration alarm which is repeated and persists if not acknowledged by the user. Participants will be instructed to respond to this alarm by checking the insulin infusion circuit for patency and performing a finger prick test. Additional instructions on managing hyperglycemia with correctional doses of insulin will be as outlined in point 5 above
- Participants will be given written instructions on dealing with technology failure. If the Dexcom G6 CGM signal is lost the device will not integrate with the pump as part of the HCL. In this circumstance, the pump will revert to non-automated insulin delivery in keeping with an individual participants' pump settings. Resumption of CGM signal and communication with the insulin pump will commence automated insulin delivery as part of the HCL system. If there is a failure in the study pump/CGM system that cannot be troubleshot virtually, the participants will need to contact the study team for a face-face visit via the telephone assistance line. All participants will be given a prescription for a long-acting basal analogue insulin in cases of pump failure to minimize the risk of DKA

  It is hoped that the technological, educational and psycho-educational interventions in this study will reduce hypoglycemia and improve awareness of hypoglycemia in participants with T1D. It is therefore possible that some participants may directly benefit from their involvement in this study. However, as not all individuals will respond to each of these interventions, no claim of benefit can be made and indeed it is possible that some participants will not derive any direct benefit at all. Participant information sheets and study advertisements will therefore make it unequivocally clear that participants do not stand to gain direct clinical benefit from their involvement, however, the final analyses from the study will be meaningful for the care of people with T1D and IAH. We have discussed risk associated with study participation with the patient stakeholder advisory group. Risks from this study were deemed reasonable and acceptable by people with T1D when weighed against the anticipated benefits. Participants will be reimbursed for their travel costs, time and out-of-pocket expenses in line with recommendations for participant reimbursement by the corresponding country’s standards for a study of this nature.

U.4. Potential Benefit to Participants

It is hoped that the technological, educational and psycho-educational interventions in this study will reduce hypoglycemia and improve awareness of hypoglycemia in participants with T1D. It is therefore possible that some participants may directly benefit from their involvement in this study. However, as not all individuals will respond to each of these interventions, no claim of benefit can be made and indeed it is possible that some participants will not derive any direct benefit at all. Participant information sheets and study advertisements will therefore make it unequivocally clear that participants do not stand to gain direct clinical benefit from their involvement, however, the final analyses from the study will be meaningful for the care of people with T1D and IAH. We have discussed risk associated with study participation with the patient stakeholder advisory group. Risks from this study were deemed reasonable and acceptable by people with T1D when weighed against the anticipated benefits. Participants will be reimbursed for their travel costs, time and out-of-pocket expenses in line with recommendations for participant reimbursement by the corresponding country's standards for a study of this nature.

U.5. Potential Benefits to Society

The results of this study will advance the field by answering fundamental questions and improving clinical pathways for the care of people with T1D and IAH. The study may inform the diabetes community as to which therapeutic interventions are best equipped both to improve impaired awareness of hypoglycemia and reduce the incidence of future severe hypoglycemic episodes. It therefore has the potential to improve quality of life among people with diabetes (and their families) and reduce healthcare costs.

U.6. Communications with Participants

IAHC research staff will maintain continuous communication with participants by email, text messages, postcards, and/or phone calls for the duration of the study. Site PIs will inform participants about how they will be contacted, encourage questions, and protect participant privacy. Researchers will inform participants that the line of communication is open and provide updated provider contact information, including an email address. The IAHC will schedule regular updates, such as through newsletters, for informing participants about study progress. Throughout the study, IAHC researchers will inform participants about where to look for published study results, including the study web site.

Clinical trial reports published in peer-reviewed scientific journals are searchable through the National Library of Medicine's PubMed database and the National Institutes of Health registry clinicaltrials.gov. The IAHC will provide participants with the study's official name or Protocol ID number so they may search the database. In addition, the IAHC will provide participants with the research team contact information should they have follow-up questions (https://www.nih.gov/health-information/nih-clinical-research-trials-you/clearly-communicating-research-results-across-clinical-trials-continuum#public-access).

When the study first becomes available in its entirety through public access, the IAHC will communicate the results with participants in a timely manner by sharing published studies, or when applicable, infographics and news releases written in patient-friendly language. Study Chairs and the IAHC Executive Committee will send participants a summary letter and a link, describing the main study findings. Each site's principal investigator will inform participants about the way in which the study results specifically apply to their own future clinical management. The NIH Public Access Policy ensures that the public has free access within a year to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central. To advance science and improve human health, NIH makes the peer-reviewed articles it funds publicly available on PubMed Central. Participants should be informed that the NIH public access policy requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to PubMed Central immediately upon acceptance for publication.

U.7. Participant Reimbursements

Visit	Visit #	Reimbursement
Screening	2	$100
Pre-clamp 1	3	$100
Clamp 1 Return Dexcom device	4	$700 $100
Randomization 1	5	$100
Pre-clamp 2	11	$125
Clamp 2 Return Dexcom device	12	$800 $100
Randomization 2	13	$100
MyHypocompass Workshop 1	TBD	$250
MyHypocompass Workshop 2	TBD	$250
MyHypocompass Workshop 3	TBD	$250
MyHypocompass 4	TBD	$250
MyHypocompass phone call	TBD	$50
HARPdoc Session 1 Session 2 Session 3 Session 4 One-on-one session 1 One-on one session 2 Follow up session 1 Follow up session 2	 TBD TBD TBD TBD TBD TBD TBD TBD	 $500 $500 $500 $500 $50 $50 $100 $100
Pre-clamp 3	19	$150
Clamp 3 Return Dexcom device	20	$900 $100
On-line Questionnaires	3, 11, 19	$100 each

In addition, each clinical site will be provided a small fund of $2,500 per year to use its discretion in compensating study participants for travel and parking.

V. Data and Specimen Storage

All participant data, including demographic, questionnaire, clinical, laboratory, and imaging data, will be stored. Stored specimens from scheduled visits include processed blood samples only. Participant identifiers will be associated with all specimens.

Data will be stored in the Department of Public Health Sciences' Data Management System (DMS). The server that the DMS database resides upon within the University Technology Center is encrypted. In addition, the DMS sits behind an Internet firewall, features role-based security, and has been assessed using OCS technical risk assessment. Data for analysis also will be extracted from the DMS, and also will be stored on an encrypted file server in the University Technology Center. Imaging data will also be stored on this encrypted file server. Because the DMS is designed to be direct data entry, limited data will be collected on paper. Clinical Centers will store paper-based data in accordance with their institution's policies. Clinical Centers will send samples to a consortium biorepository for storage. A proportion of collected samples also will be sent to an NIDDK Central Repository (https://repository.niddk.nih.gov/home/).

Data and specimens will be stored indefinitely.

Principal Investigators (PIs) and approved research staff will have access to the data and specimens. Role-based security and password-protection will be used. All samples and data transferred to the IAHC study biorepository will be under the custodianship of the IAHC PIs, although the Steering Committee will have proprietary control of, and exclusive access to, the samples and data for an agreed-upon period of time. Subsequently, samples and data, including imaging data, will be sent to the NIDDK Central Repository and available to the wider scientific community in accordance with the NIH policy on Data Sharing as well as the NIDDK policy for data sharing in multicenter and large single-center clinical studies.

The IAHC will establish an Ancillary Studies Committee and a Publications Committee to review scientific proposals from investigators within and outside of the consortium. Policy and procedures for submitting proposals, requesting data and specimens will be developed. After review of the proposals, the relevant committees will make recommendations to the IAHC Steering Committee, which will have the authority to release data and specimens.

No results from samples stored for future undetermined research will be returned to the participant.

W. References (EndNote)

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