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ORIGINAL ARTICLE

Patient-Reported Outcomes in a Randomized Trial of Closed-Loop Control: The Pivotal International Diabetes Closed-Loop Trial

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Abstract

Background: Closed-loop control (CLC) has been shown to improve glucose time in range and other glucose metrics; however, randomized trials >3 months comparing CLC with sensor-augmented pump (SAP) therapy are limited. We recently reported glucose control outcomes from the 6-month international Diabetes Closed-Loop (iDCL) trial; we now report patient-reported outcomes (PROs) in this iDCL trial.

Methods: Participants were randomized 2:1 to CLC ($N=112$) versus SAP ($N=56$) and completed questionnaires, including Hypoglycemia Fear Survey, Diabetes Distress Scale (DDS), Hypoglycemia Awareness, Hypoglycemia Confidence, Hyperglycemia Avoidance, and Positive Expectancies of CLC (INSPIRE) at baseline, 3, and 6 months. CLC participants also completed Diabetes Technology Expectations and Acceptance and System Usability Scale (SUS).

Results: The Hypoglycemia Fear Survey Behavior subscale improved significantly after 6 months of CLC compared with SAP. DDS did not differ except for powerless subscale scores, which worsened at 3 months in SAP. Whereas Hypoglycemia Awareness and Hyperglycemia Avoidance did not differ between groups, CLC participants showed a tendency toward improved confidence in managing hypoglycemia. The INSPIRE questionnaire showed favorable scores in the CLC group for teens and parents, with a similar trend for adults. At baseline and 6 months, CLC participants had high positive expectations for the device with Diabetes Technology Acceptance and SUS showing high benefit and low burden scores.

Conclusion: CLC improved some PROs compared with SAP. Participants reported high benefit and low burden with CLC. Clinical Trial Identifier: NCT03563313.

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Introduction

Over the past several years, the development of automated insulin delivery (AID) systems, also referred to as ''Closed-Loop Control'' (CLC) has become a reality. This has been accomplished by improvements in continuous glucose monitors (CGM) and insulin pumps, as well as control algorithms to modify insulin delivery based on CGM. The first system approved by the FDA in 2016 was the Medtronic 670G, which automatically delivered basal levels of insulin but not meal or correction boluses, rendering it a hybrid closed-loop (HCL) system.

More recently, the second HCL, which administered correction boluses in addition, was approved after testing in the International Diabetes Closed-Loop (iDCL) Trial.[1] This system used a CGM (Dexcom G6) that does not require fingersticks for calibration with the control algorithm embedded in the insulin pump (Control-IQ, Tandem t:slim X2).

Despite advances in CLC technology, these systems still require significant engagement from patients and families. Although a CLC system has automated features for insulin delivery to prevent hypoglycemia and avert hyperglycemia, substantial self-management remains critical for optimal use. For example, there are fundamental physical demands, such as timely changes of insulin infusion sets, inspection of infusion sites, and insertion of CGM sensors.

In addition, there remains the need to expend mental energy to operate these devices such as continued requirement to calculate meal composition and perform carbohydrate counting for accurate premeal carbohydrate gram entry into the pump for insulin bolus delivery as well as ongoing consideration of insulin management during exercise or sleep. Finally, participants and family members, across the lifespan but especially the parents of pediatric patients, expend emotional energy, including ongoing concerns about glucose values out of range, interrupted sleep due to overnight surveillance of glucose levels, system failures, forgetting how to resume manual insulin delivery if the system were to fail, and financial stress associated with the cost of treatment, to name a few. Finally, people may have unrealistic expectations related to devices that are named CLC or AID.

Without realistic expectations, persons with type 1 diabetes (T1D) beginning such systems may be disappointed and discontinue use or expend less effort than needed for successful implementation and continued use.[2–4] Thus, it is important to understand patient perspectives on such systems to identify issues in acceptance of these devices.

Therefore, in addition to glucose control outcomes, the pivotal trial was designed to recognize that, from the users' perspective, there are numerous nonglycemic outcomes that determine whether or not a CLC system has a positive impact on their lives. Equally important is to demonstrate that CLC use does not add to the burden of diabetes management or have a negative impact on quality of life. Thus, the trial included a number of patient-reported outcome (PRO) measures to assess user experience with the technology and the impact of system use on dimensions of quality of life that are meaningful to most individuals living with T1D.

The PROs studied addressed diabetes distress, fear of hypoglycemia, confidence with managing hypoglycemia, avoidance of hyperglycemia, and acceptance of the advanced technologies to assess the efficacy and benefit/burden of CLC compared with sensor-augmented pump (SAP). Pivotal studies examining CLC, employing randomized controlled trial (RCT) methods, large numbers of participants representing a wide range of ages, and long-term free range use, have not sufficiently studied and/or reported PROs: this study thus fills an important gap in this scientific literature.

Methods

The iDCL trial

The trial was conducted at seven U.S. centers after approval by a central Institutional Review Board. Details of the study design and clinical outcomes have been previously published, with the full protocol available.[1] In brief, participants 14–71 years old with T1D were randomized 2:1 to either CLC or SAP treatment for 6 months. Outcome measures, including hemoglobin A1c (HbA1c), CGM metrics, and questionnaires, were obtained at baseline, at 3 months, and at the end of the trial. The primary outcome was CGM time in range 70–180 mg/dL (3.9–10.0 mmol/L) throughout the 6-month period.

All participants used the study CGM (Dexcom G6). The SAP group used their personal or study provided pump without the CLC system. Predictive low-glucose suspend system (PLGS) users were excluded from the study. The CLC group used the Control-IQ system with the CLC algorithm embedded on the study insulin pump (t:slim X2 pump; Tandem Diabetes Care).

Patient-reported outcomes

All PRO questionnaires used are listed in Table 1. The psychometric properties, including reliability and validity of most of these measures, are well documented in the literature and references are provided that contain specific statistical findings and coefficients. Additional information regarding psychometric properties is provided for those measures that have not received such extensive study. All participants (adult and pediatric) completed these questionnaires. We have described instances where subjects aged 14–18 years and their parents answered a different questionnaire version in context in succeeding sections.

Hypoglycemia Fear Survey

The Hypoglycemia Fear Survey (HFS-II)[5] assesses fear of hypoglycemia and was administered to adults and adolescents, and their parents. The adult version has 23 items rated on a 0–4 scale and generates a total score and two subscale scores (Behavior and Worry). The Behavior Subscale has two factors, including a ''Maintain High BG'' factor that reflects behaviors aimed at keeping glucose levels higher to prevent hypoglycemia and an ''Avoidance'' factor reflecting other behaviors aimed at preventing hypoglycemia. The Parent and Adolescent versions[6] include 25 items rated on the same scale generating Total, Behavior Subscale and Worry Subscale scores. Higher scores indicate more fear.

Table 1. Summary of Questionnaires and Associated Total Score Values at Randomization and Follow-Up Visits

	Randomization				*13 Weeks*						*Final visit/26 weeks*					
	CLC		*SAP*		*CLC*[b]		*SAP*[b]		*Mean adjusted treatment difference CLC-SAP (95% CI)*[c]	P[c]	*CLC*		*SAP*		*Mean adjusted treatment difference CLC-SAP (95% CI)*[c]	P[c]
Questionnaire[a]	N	*Score*[d]	N	*Score*[d]	N	*Score*[d]	N	*Score*[d]			N	*Score*[d]	N	*Score*[d]		
Diabetes Distress, Adult	112	1.8 (0.6)	56	1.8 (0.7)	112	1.7 (0.6)	56	1.9 (0.7)	−0.17 (−0.33 to 0)	0.04	111	1.7 (0.6)	55	1.9 (0.8)	−0.11 (−0.31 to 0.09)	0.30
Diabetes Distress, Parent	31	1.2 (0.7)	17	1.0 (0.5)	31	1.0 (0.8)	17	1.2 (0.7)	−0.34 (−0.94 to 0.26)	0.29	31	1.0 (0.7)	15	1.1 (0.6)	−0.26 (−0.71 to 0.19)	0.29
Hypoglycemia Fear, Adult	81	39 (14)	39	42 (18)	81	33 (13)	39	38 (18)	−2.7 (−7.0 to 1.6)	0.23	80	33 (12)	39	38 (18)	−3.1 (−7.8 to 1.6)	0.23
Hypoglycemia Fear, Teen	31	36 (12)	17	38 (13)	31	33 (11)	17	35 (13)	−0.5 (−6.5 to 5.5)	0.82	31	32 (10)	16	31 (16)	3.3 (−3.2 to 9.8)	0.30
Hypoglycemia Fear, Parent	31	44 (13)	17	40 (12)	31	35 (13)	17	38 (11)	−6.0 (−14.0 to 2.1)	0.17	31	33 (14)	15	36 (15)	−5.7 (−16.2 to 4.7)	0.30
Clarke Hypoglycemia Awareness	112	1 (0, 2)	56	1 (0, 3)	112	1 (0, 3)	56	2 (0, 3)	0.0 (−0.5 to 0.5)	0.84	111	1 (0, 3)	55	2 (0, 3)	0.0 (−0.6 to 0.5)	0.81
Hyperglycemia Avoidance	112	39 (8)	56	39 (10)	112	37 (9)	56	37 (11)	−0.4 (−3.1 to 2.3)	0.72	111	379 (9)	55	37 (11)	0.4 (−2.6 to 3.3)	0.74
INSPIRE Survey, Adult	81	80 (13)	39	86 (13)	81	85 (14)	39	85 (14)	5.0 (−0.4 to 10.4)	0.09	80	87 (14)	39	86 (13)	5.1 (−0.6 to 10.9)	0.09
INSPIRE Survey, Teen	31	79 (10)	17	79 (12)	31	82 (16)	17	73 (10)	9.2 (−1.4 to 19.8)	0.10	31	87 (13)	16	74 (12)	12.0 (1.9 to 22.0)	0.02
INSPIRE Survey, Teen Parent	31	79 (10)	17	78 (14)	30	83 (15)	17	76 (13)	6.0 (−5.5 to 17.4)	0.30	31	87 (13)	15	76 (12)	10.8 (1.8 to 19.8)	0.02
Technology Expectation/ Acceptance[e]	112	147 (19)	—	—	111	152 (20)	—	—	—	—	111	155 (19)	—	—	—	—
SUS[e]	—	—	—	—	110	85 (12)	—	—	—	—	109	87 (12)	—	—	—	—

[a]Hypoglycemia Confidence Scale assessed at randomization, 13 weeks, and 26 weeks, but no total score defined for instrument; refer to question-specific results in Table 5.
[b]One participant in SAP group and one participant in CLC group did not complete the 26-week visit within the prespecified window and the 26-week values were not included in the analyses.
[c]Adjusted for baseline value of the dependent variable, age, prior CGM use, prior pump use, and clinical center (random effects). *P* values adjusted for multiplicity using the FDR.
[d]Questionnaire scores presented as mean (SD) except for Clarke Hypoglycemia Awareness score, presented as median (IQR).
[e]Closed-loop treatment group only.

CI, confidence interval; CLC, closed-loop control; CGM, continuous glucose monitor; FDR, false discovery rate; SAP, sensor-augmented pump; SD, standard deviation; SUS, System Usability Scale.

Diabetes Distress Scale

The Diabetes Distress Scale (DDS)[7] measures diabetes-related distress and was administered to adult and adolescent participants (14–18 years) and their parents. The questionnaire administered to adults and teens consists of 28 items rated on a 1–6 Likert Scale with seven subscales, including Powerlessness, Management, Hypoglycemia, Negative social perception, Eating, Physician, and Friends/family. The Parent DDS[8] includes 21 items rated 0–4 with four subscales, including Personals, Teen management, Parent/teen relationship, and Health care team. Higher scores indicate more distress.

Clarke's Hypoglycemia Awareness Survey

This scale includes eight questions that assess the extent to which hypoglycemia symptoms are experienced and at what glycemic thresholds.[9] The survey score ranges for 0–7 with scores of four or higher indicating impaired awareness of hypoglycemia.

Hypoglycemia Confidence Scale

The Hypoglycemia Confidence Scale (HCS)[10] measures the degree to which people with diabetes are confident regarding their ability to manage hypoglycemia. The scale includes nine items rated on a 0–3 scale, from not at all confident to very confident. Higher scores indicate more confidence.

Hyperglycemia Avoidance Scale

The Hyperglycemia Avoidance Scale (HAS)[11] includes 21 items rated on a 0–4 scale and generates a total score and four subscale scores, including immediate action to lower high glucose; worry about hyperglycemia, preference to keep glucose lower; and strategies to avoid extreme high blood glucose (BG) Higher scores indicate higher hyperglycemia worry and avoidance behavior.

INSPIRE

The INSPIRE[12] questionnaires measures user experience with AID technologies. The adult, adolescent, and parent versions contain 22, 17, and 21 items, respectively, which are rated on a 0–4 scale. Total scores are calculated by obtaining a mean score across items, then multiplying the mean by 25 to obtain a score from 0 to 100. Higher scores indicate greater positive expectations for or experience with AID technology.

Only the CLC group answered the following surveys.

Technology Expectation Survey

This questionnaire includes 36 items rated on a 5-point bipolar scale and contains two subscales: 19 items reflecting the benefits and 17 items reflecting the burdens associated with CLC that the user expects to experience.[13] This measure is an adaptation of the Technology Acceptance Survey (Technology Acceptance Survey section) with the same items only worded differently to assess expectations rather than experience, that is, ''I expect Control IQ to be more of a hassle than my usual diabetes management'' versus ''Control IQ was more of a hassle than my usual diabetes management.''

In addition, three face-valid items were added to this questionnaire and were rated on a 5-point Likert scale to assess user perceptions of ease of use, usefulness, and trust they expected and experienced with the system (i.e., To what extent do you expect to/did you find Control IQ easy to use? To what extent do you expect/did you find Control IQ useful in managing your diabetes? To what extent do you expect to/did you trust Control IQ?). These three face-valid questions were added for all participants.

Technology Acceptance Survey

The original version of this questionnaire was developed in a study of the bi-hormonal CLC system but can be adapted to any specific CLC device.[13] This questionnaire includes the identical items and subscales described earlier for the Expectation Survey but is worded to reflect the actual experiences of participants during system use. The three face-valid items on usability, usefulness, and trust were also added to this survey.

System Usability Survey

This instrument measures satisfaction and ease of device use in general and includes 10 items rated on a 0–4 point bipolar scale.[14] It is widely used in industry to assess user experience with products during the development stage. A score of 68 is considered average with higher scores indicating a positive response and lower scores indicating a negative response.

Data analyses

PROs between the two treatment arms were compared using a linear mixed effects regression model that included adjustment for the baseline level of PROs, age, prior continuous glucose monitor and pump use, and clinical center (random effect). Descriptive statistics include means with standard deviations (SD) and medians with interquartile ranges (IQRs), depending on the distribution of data. Because of the bounded nature of the questionaries scores (in general on a 5-point scale), means (SD) were used for these outcomes. All P values and confidence intervals were adjusted for multiplicity using the false discovery rate. All P values are two-tailed.

In a post hoc analysis, we explored whether baseline psychosocial characteristics (i.e., Diabetes Distress and Fear of Hypoglycemia scores) could predict device usage measures and time in range 70–<180 mg/dL (TIR). The approach included inspection of plots of the baseline scores versus device usage and TIR in months 1–3 and 4–6 as well as stratification according to baseline tertiles (low, medium, and high degree) of questionnaire scores. Statistical testing for these analyses were not performed as there was no prespecification. The study was designed to have a >90% statistical power to detect a 7.5% increase in % time in range 70–180 mg/dL from SAP to CLC. We estimate the actual power to be substantially <90% for outcomes with large variance such as questionnaires or for subgroups such as adults and teens; but we have refrained from calculating any such power for secondary outcomes after the study was finalized and analyses completed.

Analyses were performed with SAS software, version 9.4 (SAS Institute).

Results

The study randomly assigned participants to SAP ($n = 56$) or CLC ($n = 112$) with 105 adults (25–71 years old) and 63

younger adults and teens (14–24 years old). Baseline characteristics are described in Table 2. Participant flow through study is described in the RCT article.[1]

Treatment groups were well matched for age (33 ± 16 years CLC vs. 33 ± 17 years SAP), gender (female CLC 54% vs. SAP 48%), diabetes duration (CLC 17 IQR 8–28 years vs. SAP 15 IQR 7–23 years), insulin pump use (CLC 80% vs. SAP 78%), CGM use at baseline (CLC 70% vs. SAP 71%), and A1c (CLC 7.4% ± 1.0% [57 ± 10.9 mmol/mol] vs. 7.4 ± 0.8% [57 ± 8.7 mmol/mol]). The previously reported primary outcomes demonstrated an 11% increase (+2.6 h daily) in glucose TIR (70–180mg/dL) in the CLC group (71% ± 12%) compared with the SAP group (59% ± 14%) with all glycemic outcomes favoring the CLC group.[1]

Total scores from the PRO questionnaires are shown in Table 1.

Diabetes Distress Scale

For adults, total DDS scores were significantly higher in the SAP group compared with the CLC group at 3 months but not at 6 months (Table 3; $P = 0.04$). Subscale scores showed that SAP group scores were significantly higher than the CLC group on the powerless subscale at 3 months ($P = 0.02$) but not at 6 months. Of the remaining DDS subscale scores, there were no significant differences between the two groups. In parents, there were no significant differences between groups in DDS scores at 3 or 6 months (Table 4).

Table 2. Participant Characteristics at Baseline by Treatment Group

	CLC (treatment group) (N = *112*)	*SAP (control group)* (N = *56*)
Age (years)		
Mean ± SD	33 ± 16	33 ± 17
≥18 years, *n* (%)	81 (72)	39 (70)
<18 years, *n* (%)	31 (28)	17 (30)
Diabetes Duration (years), median (IQR)	17 (8, 28)	15 (7, 23)
Continuous glucose monitor use at enrollment *n* (%)	78 (70)	40 (71)
BMI (kg/m^2) median (IQR)	25 (23, 29)	25 (22, 28)
Sex: female, *n* (%)	54 (48)	30 (54)
Race: white, *n* (%)[a]	94 (86)	53 (95)
Hispanic or Latino Ethnicity, *n* (%)	13 (12)	5 (9)
Annual household income,[b] *n* (%)		
<$50,000	10 (11)	2 (4)
$50,000 to <$100,000	24 (27)	18 (36)
≥$100,000	55 (62)	30 (60)
Highest education level,[c] *n* (%)		
<Bachelor's degree	16 (14)	13 (23)
Bachelor's degree	51 (46)	21 (38)
Advanced degree	44 (40)	22 (39)
Baseline glycated hemoglobin, mean ± SD	7.4 ± 1.0	7.4 ± 0.8

[a]Three patients in the treatment group did not provide race information.

[b]Twenty-three patients in the treatment group and six in the control group did not provide income information.

[c]Highest level completed by patient, or by primary caregiver if patient <18 years. One patient in the treatment group did not provide education information.

BMI, body mass index; IQR, interquartile range.

Hypoglycemia Fear Survey

Total HFS-II scores for adults showed no differences between SAP and CLC groups at 3 or 6 months (Table 3). Worry subscale scores also did not differ between study groups. However, behavior subscale scores were lower (more favorable) in the CLC group at 6 months ($P = 0.02$). Scores on the two factors of the behavior subscale were examined and showed lower (more favorable) scores in the CLC group on items reflecting tendencies to maintain higher BG levels in certain situations to avoid hypoglycemia (mean = 25 ± 18) compared with the SAP group (mean = 35 ± 26). HFS-II scores did not differ in either group for adolescents or parents.

Hypoglycemia Awareness Scale (Clarke)

At baseline, 13% and 14% of participants had scores indicating reduced hypoglycemia awareness in the CLC and SAP groups, respectively. At 3 months, proportions of participants with reduced awareness remained similar in both groups. At study's end, there was no statistical difference in survey scores between groups or the proportion of participants with reduced awareness (Table 4).

Hypoglycemia Confidence Scale

Whereas CLC increased confidence in eight of the nine self-care areas (by 2%–23%) at 6 months compared with baseline, confidence increased in two areas in the SAP group (exercise and sleep) but declined in six areas (by 1%–16%). No statistical testing was undertaken. Confidence with managing hypoglycemia when alone did not change in either group (the one area in which confidence did not increase in the CLC group). Findings were fairly similar at 3 months (Tables 5 and 6).

Hyperglycemia avoidance scale

None of the scores differed significantly between the two groups at 3 or 6 months (Table 4).

INSPIRE

For adults, scores on the INSPIRE survey were not significantly different comparing the two groups ($P = 0.09$ at both 3 and 6 months; Table 1). For surveys completed by adolescents and their parents separately, CLC group scores were significantly higher than SAP scores at 6 months for both adolescents and parents ($P = 0.02$ for both).

Technology expectations and acceptance

At baseline, ratings indicated that expected benefits of CLC were high (Table 1 and 4, mean = 4.0 ± 0.5) and expected barriers were low (mean = 2.0 ± 0.6). At 3 months, ratings indicated a positive user experience with high perceived benefits (mean = 4.2 ± 0.6) and low perceived burdens (mean = 1.8 ± 0.6). This same pattern was evident at 6 months (mean benefit rating = 4.3 ± 0.6, mean burden rating = 1.8 ± 0.6), indicating that participants experienced far more benefits than burdens using the system. The three additional questions that

Table 3. Adult Diabetes Distress Scale and Adult/Teen Hypoglycemia Fear Survey Results with Subscale Scores

	Randomization				*13 Weeks*						*Final visit/26 weeks*					
	CLC		*SAP*		*CLC*[a]		*SAP*[a]		*Mean adjusted treatment difference CLC-SAP (95% CI)*[b]	P[b]	*CLC*		*SAP*		*Mean adjusted treatment difference CLC-SAP (95% CI)*[b]	P[b]
Questionnaire/subscale	N	*Score*[c]	N	*Score*[c]	N	*Score*[c]	N	*Score*[c]			N	*Score*[c]	N	*Score*[c]		
Diabetes Distress, Adult (total)	112	1.8 (0.6)	56	1.8 (0.7)	112	1.7 (0.6)	56	1.9 (0.7)	–0.17 (–0.33 to 0)	0.04	111	1.7 (0.6)	55	1.9 (0.8)	–0.11 (–0.31 to 0.09)	0.30
Powerless	112	2.3 (1.0)	56	2.3 (1.0)	112	2.2 (0.9)	56	2.6 (1.1)	–0.34 (–0.64 to 0.04)	0.02	111	2.2 (1.0)	55	2.5 (1.1)	–0.22 (–0.55 to 0.11)	0.23
Management Distress	112	1.8 (0.8)	56	1.8 (0.9)	112	1.6 (0.7)	56	1.8 (0.8)	–0.21 (–0.47 to 0.04)	0.10	111	1.7 (0·.)	55	1.8 (0.8)	–0.14 (–0.42 to 0.13)	0.30
Hypoglycemia Distress	112	1.7 (0.8)	56	1.8 (1.0)	112	1.6 (0.7)	56	1.8 (1.0)	–0.11 (–0.34 to 0.12)	0.32	111	1.6 (0.7)	55	1.8 (1.0)	–0.17 (–0.43 to 0.09)	0.23
Negative Social Perception	112	1.6 (0.8)	56	1.6 (1.0)	112	1.6 (0.7)	56	1.6 (0.9)	–0.01 (–0.23 to 0.21)	0.89	111	1.6 (0.8)	55	1.6 (1.0)	0.06 (–0.18 to 0.30)	0.55
Eating Distress	112	2.0 (0.8)	56	2.1 (1.1)	112	2.0 (0.9)	56	2.2 (1.2)	–0.18 (–0.49 to 0.13)	0.29	111	2.1 (1.0)	55	2.1 (1.0)	0.05 (–0.31 to 0.41)	0.74
Physician Distress	112	1.3 (0.6)	56	1.3 (0.7)	112	1.2 (0.5)	56	1.3 (0.8)	–0.12 (–0.33 to 0.09)	0.29	111	1.2 (0.4)	55	1.4 (0.9)	–0.20 (–0.43 to 0.02)	0.09
Friends/Family Distress	112	1.9 (1.0)	56	1.7 (0.7)	112	1.7 (0.8)	56	1.8 (1.0)	–0.21 (–0.49 to 0.07)	0.17	111	1.7 (0.9)	55	1.8 (1.0)	–0.10 (–0.40 to 0.21)	0.49
Hypoglycemia Fear, Adult (total)	81	39 (14)	39	42 (18)	81	33 (13)	39	38 (18)	–2.7 (–7.0 to 1.6)	0.23	80	33 (12)	39	38 (18)	–3.1 (–7.8 to 1.6)	0.23
Behavior	81	51 (12)	39	55 (16)	81	44 (13)	39	51 (15)	–4.4 (–9.9 to 1.1)	0.12	80	43 (12)	39	52 (15)	–6.5 (–11.7 to –1.2)	0.02
Maintain High BG	81	34 (19)	38	38 (24)	81	25 (19)	39	35 (22)	–	–	80	25 (18)	39	35 (26)	—	—
Worry	81	29 (18)	39	32 (23)	81	25 (16)	39	29 (23)	–1.7 (–6.9 to 3.5)	0.49	80	25 (15)	39	27 (22)	–0.6 (–6.7 to 5.6)	0.80
Hypoglycemia Fear, Teen (total)	31	36 (12)	17	38 (13)	31	33 (11)	17	35 (13)	–0.5 (–6.5 to 5.5)	0.82	31	32 (10)	16	31 (16)	3.3 (–3.2 to 9.8)	0.30
Behavior	31	56 (15)	17	50 (16)	31	52 (13)	17	50 (15)	–2.7 (–11.6 to 6.3)	0.52	31	53 (14)	16	45 (14)	3.1 (–5.8 to 12.1)	0.46
Maintain High BG	31	36 (23)	17	29 (21)	31	34 (20)	17	28 (20)	–	—	31	33 (21)	16	26 (22)	—	—
Worry	31	23 (16)	17	30 (16)	31	20 (16)	17	25 (17)	0.7 (–8.1 to 9.6)	0.81	31	19 (14)	16	22 (18)	3.1 (–4.7 to 11.0)	0.39

[a]One participant in SAP group and one participant in CLC group completed the 26-week visit outside the prespecified window and the 26-week values were excluded from analyses.
[b]Adjusted for baseline value of the dependent variable, age, prior CGM use, prior pump use, and clinical center (random effects). *P* values adjusted for multiplicity using the FDR.
[c]Questionnaire scores presented as mean (SD).
BG, blood glucose.

Table 4. Additional Patient-Reported Outcome Questionnaire Subscale Scores

	Randomization				*13 Weeks*						*Final visit/26 weeks*					
	CLC		*SAP*		*CLC*[a]		*SAP*[a]		*Mean adjusted treatment difference CLC-SAP (95% CI)*[b]	P[b]	*CLC*		*SAP*		*Mean adjusted treatment difference CLC-SAP (95% CI)* [b]	P[b]
Questionnaire/ subscale	N	*Score*[c]	N	*Score*[c]	N	*Score*[c]	N	*Score*[c]			N	*Score*[c]	N	*Score*[c]		
Diabetes Distress, Parent (total)	31	1.2 (0.7)	17	1.0 (0.5)	31	1.0 (0.8)	17	1.2 (0.7)	−0.34 (−0.94 to 0.26)	0.29	31	1.0 (0.7)	15	1.1 (0.6)	−0.26 (−0.71 to 0.19)	0.29
Personal Distress	31	1.2 (0.7)	17	0.9 (0.6)	31	1.0 (0.9)	17	1.1 (0.7)	−0.27 (−0.92 to 0.37)	0.37	31	1.1 (0.8)	15	1.2 (0.7)	−0.28 (−0.83 to 0.27)	0.30
Teen Management Distress	31	1.3 (0.7)	17	1.2 (0.7)	31	1.0 (0.9)	17	1.3 (0.6)	−0.32 (−0.98 to 0.33)	0.31	31	1.1 (0.8)	15	1.3 (0.5)	−0.20 (−0.71 to 0.31)	0.40
Parent/Teen Relationship Distress	31	1.3 (0.7)	17	1.0 (0.5)	31	1.0 (0.8)	17	1.3 (0.8)	−0.39 (−1.03 to 0.25)	0.26	31	1.0 (0.7)	15	1.1 (0.7)	−0.24 (−0.72 to 0.23)	0.30
Health care Team Distress	31	0.9 (0.7)	17	0.4 (0.5)	31	0.7 (0.8)	17	0.7 (0.8)	−0.28 (−1.00 to 0.43)	0.39	31	0.7 (0.6)	15	0.5 (0.4)	−0.10 (−0.56 to 0.36)	0.60
Clarke Hypoglycemia Awareness (total)	112	1 (0, 2)	56	1 (0, 3)	112	1 (0, 3)	56	2 (0, 3)	0.0 (−0.5 to 0.5)	0.84	111	1 (0, 3)	55	2 (0, 3)	0.0 (−0.6 to 0.5)	0.81
Reduced Awareness, *n* (%)	112	14 (13%)	56	8 (14%)	112	17 (15%)	56	8 (14%)	—	—	111	18 (16%)	55	7 (13%)	—	—
Uncertain, *n* (%)	81	12 (11%)	56	7 (13%)	112	12 (11%)	56	6 (11%)	—	—	111	14 (13%)	55	11 (20%)	—	—
Aware, *n* (%)	81	86 (77%)	56	41 (73%)	112	83 (74%)	56	42 (75%)	—	—	111	79 (71%)	55	37 (67%)	—	—
Hyperglycemia Avoidance (total)	112	39 (8)	56	39 (10)	112	37 (9)	56	37 (11)	−0.4 (−3.1 to 2.3)	0.72	111	379)	55	37 (11)	0.4 (−2.6 to 3.3)	0.74
Immediate action	112	14 (2)	56	13 (2)	112	13 (2)	56	13 (2)	−0.2 (−1.1 to 0.7)	0.55	111	14 (3)	55	13 (2)	0.2 (−0.7 to 1.2)	0.56
Worry	112	14 (5)	56	14 (6)	112	13 (6)	56	13 (6)	−0.4 (−2.1 to 1.3)	0.55	111	12 (6)	55	13 (6)	−0.4 (−2.3 to 1.5)	0.60
Low-BG preference	112	7 (3)	56	7 (2)	112	6 (3)	56	6 (3)	0 (−0.9 to 1.0)	0.97	111	7 (3)	55	6 (3)	0.3 (−0.8 to 1.3)	0.55
Avoid extremes	112	5 (2)	56	5 (3)	112	4 (2)	56	4 (2)	0.3 (−0.5 to 1.1)	0.49	111	5 (2)	55	4 (3)	0.3 (−0.7 to 1.2)	0.53
Technology Expectation/ Acceptance (total)	112	143.9 (18.6)	—	—	109	149.2 (19.8)	—	—	—	—	111	152.3 (18.8)	—	—	—	—
Efficacy score	112	12.6 (1.6)	—	—	109	13.5 (1.8)	—	—	—	—	111	13.8 (1.4)	—	—	—	—
Benefit	112	4.0 (0.5)			109	4.2 (0.6)					111	4.3 (0.6)				
Barrier	112	2.0 (0.6)			109	1.8 (0.6)					111	1.8 (0.6)				
SUS (total)					110	85 (12)					109	87 (12)				
Benefit					110	4.5 (0.5)					109	4.5 (0.5)				
Barrier					110	1.7 (0.6)					109	1.6 (0.6)				

[a]One participant in SAP group and one participant in CLC group completed the 26-week visit outside the prespecified window and the 26-week values were excluded from analyses.
[b]Adjusted for baseline value of the dependent variable, age, prior CGM use, prior pump use, and clinical center (random effects). *P* values adjusted for multiplicity using the FDR.
[c]Questionnaire scores presented as mean (SD), median (IQR), or *n* (%) as indicated.

Table 5. Hypoglycemia Confidence Scale Individual Question Results

	% Responding "very confident" to question					
	Randomization		13 Weeks		Final visit/26 weeks	
Question	CLC (%)	SAP (%)	CLC (%)	SAP (%)	CLC (%)	SAP (%)
When you are exercising?	32	27	41	29	43	29
When you are sleeping?	22	20	36	16	45	27
When you are driving?	58	53	60	50	60	49
When you are in social situations?	50	60	55	52	59	44
When you are alone?	48	42	59	46	61	42
Avoid serious problems due to hypoglycemia?	49	43	46	41	53	29
Catch and respond to hypoglycemia before your blood sugars get too low?	47	39	49	41	51	38
Continue to do the things you really want to do in your life, despite the risks of hypoglycemia?	56	52	59	46	61	38
If you have a spouse or partner: What is your best guess about how confident your spouse or partner feels about your ability to avoid serious problems due to hypoglycemia?	56	39	47	36	48	32

directly assessed user perceived ease of use, usefulness, and trust in the system yielded mean scores of 4.2, 4.5, and 4.6, respectively, indicating a positive experience.

System Usability Scale score

System Usability Scale (SUS) score results were similarly positive with high perceived benefit at 3 and 6 months (Table 4; mean = 4.5 ± 0.35 for both) and low burden at the same time points (1.7 ± 0.6 and 1.6 ± 0.6, respectively), equating to a SUS score of 87 ("excellent" usability) at 6 months (Table 1).

Descriptive analyses of CGM use, CLC use, and TIR in each tertile of Diabetes Distress and Fear of Hypoglycemia.

Supplementary Figures S1–S3 and Supplementary Table S1 show these data in CLC and SAP groups at baseline and during the months 1–3 and 4–6, respectively. In general, use of CGM was impressively high but tended to be lower in the SAP compared with the CLC group. TIR for SAP group participants was lower with higher baseline diabetes distress in both the first and the last 3 months of the study.

Discussion

This pivotal trial of CLC for T1D evaluated PROs in addition to primary and secondary glycemic outcome measures. The analyses of PROs are especially important and relevant given the significant burden and attention to detail required for successful utilization of CLC systems. To achieve widespread adoption and long-term use of this technology, it is important that CLC does not have a negative impact on quality of life or sense of well-being in people living with diabetes. In addition to satisfaction and user experience, the PROs we studied included those assessing constructs relevant to people with diabetes, including multiple dimensions of diabetes-related distress, fear of hypoglycemia, confidence with hypoglycemia management, and hyperglycemia avoidance.

Table 6. Hypoglycemia Confidence Scale Individual Question Mean Scores

	Mean response score					
	Randomization		13 Weeks		Final visit/26 weeks	
Question	CLC	SAP	CLC	SAP	CLC	SAP
When you are exercising?	2.1	2.1	2.2	1.9	2.3	1.9
When you are sleeping?	2.0	2.0	2.2	1.9	2.3	1.9
When you are driving?	2.5	2.3	2.5	2.4	2.6	2.3
When you are in social situations?	2.5	2.5	2.5	2.4	2.6	2.4
When you are alone?	2.4	2.3	2.5	2.4	2.6	2.3
Avoid serious problems due to hypoglycemia?	2.4	2.4	2.4	2.3	2.5	2.1
Catch and respond to hypoglycemia before your blood sugars get too low?	2.3	2.3	2.4	2.3	2.4	2.3
Continue to do the things you really want to do in your life, despite the risks of hypoglycemia?	2.4	2.4	2.5	2.4	2.5	2.2
If you have a spouse or partner: What is your best guess about how confident your spouse or partner feels about your ability to avoid serious problems due to hypoglycemia?	2.4	2.1	2.4	2.1	2.4	2.1

An important finding from this study is that CLC use was not associated with any negative impact on any of the PROs measured. In fact, the only negative psychological outcome observed in the study occurred in the SAP group, whose diabetes distress, especially the feeling of powerlessness, was significantly higher at 3 months after randomization. One interpretation for this finding is that individuals coming into the study were highly motivated to use the CLC system and finding out they would not have this opportunity during the RCT resulted in disappointment and distress, even though they were aware they would receive the CLC system after 6 months. In contrast, the CLC group indicated no negative changes in diabetes-related emotional status or concerns.

In addition, individuals in the CLC group reported a significant decrease in fear of hypoglycemia at the end of the study on the behavior subscale scores that assess the tendency to prevent hypoglycemia by maintaining higher glucose levels, especially when doing important tasks such as attending meetings or social events. Research suggests that this behavioral strategy for coping with hypoglycemia can have a negative impact on diabetes control. If people using CLC are able to avoid these behaviors because they trust the automated system to protect them from hypoglycemia, this could have beneficial clinical implications with the potential for improved time in target range.

The INSPIRE survey results were also positive, yielding significant differences for youth and parents in the CLC group compared with the SAP group after 6 months, with a similar favorable trend for the adults in CLC group compared with SAP group at 3 months. These findings confirm the positive user experience of participants receiving CLC, especially among the younger ''tech-savvy'' participants who have grown up in a technology era, giving them a fundamental comfort with such devices.

The Technology Acceptance survey that measures user perceived burdens in addition to benefits showed high levels of experienced benefits with low levels of experienced burden with CLC. Thus, in this patient population, the perceived benefits of CLC use outweighed the perceived burden, an important predictor of health care decisions to adopt and maintain new treatment behaviors. Participants in the CLC group also gave high ratings to the three items assessing the basic dimensions of technology acceptance, which are ease of use, overall usefulness, and trust. Taken together, the high level of satisfaction that persisted through the 6-month trial indicates the likelihood of long-term acceptance of the CLC system. Initial reports of real-world technology acceptance and other PROs with use of Control-IQ technology have also been very positive.[15]

We performed exploratory analyses of device use and glucose control outcomes across the baseline tertiles of patient-reported diabetes distress and fear of hypoglycemia in the two study groups as a means to understand potential psychosocial patient-predictors of device success. Overall, high CGM use in both groups was encouraging. However, participants in the SAP group with higher baseline diabetes distress had lower TIR in the study indicating that the potential impact of diabetes-related distress on successful use of different technologies should be considered in future studies. Nonetheless, it is encouraging that CLC system use and associated glycemic outcomes were similar across the range of baseline diabetes distress and fear of hypoglycemia.

There are a number of limitations to this investigation of PROs. First, several different versions of surveys were administered to subsets of the study sample (i.e., adults, youth, and parents) reducing our potential power to discern statistically or clinically meaningful differences between the groups. Second, although the trial included a broad range of eligibility criteria with respect to glycemic control and history of acute complications, it remains likely that study participants represent early adopters of diabetes technology, some of whom had participated in previous CLC studies (not an exclusion in this study). Future evaluations are needed of PROs once CLC is implemented more widely in the general population with T1D.

It is also possible that participants felt pressure to give socially desirable survey responses. To avoid such bias, questionnaires were generally administered in private, using a computer, avoiding the need for interactions with study staff. In addition, surveys can have floor or ceiling effects, limiting the chance to discern meaningful change. Thus, it is notable that CLC use did not increase diabetes distress; on the contrary, there was evidence of some increase in distress in the SAP group not randomized to receive CLC.

Third, there is the possibility that these participants may have lower levels of diabetes distress and other emotional sequelae associated with T1D. However, Diabetes Distress scores were >1.9 in approximately one-third of participants. Previous studies have defined scores >2.0 as the clinical cutoff for clinically significant levels of distress, which is found in about 40% of people with T1D.

There were some aspects of the patient experience that we did not study. For instance, subjects did not announce exercise in the system even though they indicated to site investigators that they were exercising more often than they were announcing. We did not specifically evaluate the sleep mode of the system. The study population was different from the U.S. population of patients with T1D.[16] CGM use in the T1D Exchange for the period from 2016 to 2018 was 27.2% and MDI use was 38.6%. The mean A1c of the current sample was also better than the U.S. population at the time of the study.[16]

In addition, the income and educational achievement of the participants was better than the general population of people living with T1D in the United States. Finally, the study was underpowered to detect differences in PROs. This issue will need to be addressed in future study involving CLC.

Clearly, more research is needed to assess the impact of CLC on quality of life, although one can be encouraged by the high satisfaction scores and the observation of decreased fear of hypoglycemia and increased hypoglycemia confidence, likely mediated by reduced time below range (i.e., hypoglycemia) associated with CLC. Given the burgeoning development of advanced diabetes technologies, there will be many opportunities to assess PROs. Nonetheless, it remains important to provide realistic expectations regarding use of these devices as technological improvements are likely to be incremental and will continue to require user training and engagement.

Future research can identify factors that can contribute to widespread adoption and beneficial outcomes for people with diabetes. These findings provide preliminary evidence that users of this CLC technology did not experience an increase

in perceived burdens associated with diabetes management but rather high levels of perceived benefits, including reduced fear of hypoglycemia.

Authors' Contributions

Y.C.K. researched data and wrote/edited the article. D.R. performed statistical analyses and wrote/edited the article. L.M.L., S.A.B., J.E.P., L.E., C.J.L., L.H.M., B.P.K., J.W.L., R.W.B., and L.G.-F. researched data, contributed to discussion, and reviewed/edited the article.

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Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Table S1

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