BMC Endocrine Disorders

RESEARCH

Open Access

Use of a decision support tool and quick start onboarding tool in individuals with type 1 diabetes using advanced automated insulin delivery: a single-arm multi-phase intervention study

Shekhar Sehgal[1,2], Martin De Bock[3,4], Benyamin Grosman[5], Jonathan Williman[3], Natalie Kurtz[5], Vanessa Guzman[5], Andrea Benedetti[5], Anirban Roy[5], Kamuran Turksoy[5], Magaly Juarez[5], Shirley Jones[1], Carla Frewen[1], Antony Watson[3], Barry Taylor[1] and Benjamin J. Wheeler[1,6*]

Abstract

Background Multiple clinician adjustable parameters impact upon glycemia in people with type 1 diabetes (T1D) using Medtronic Mini Med 780G (MM780G) AHCL. These include glucose targets, carbohydrate ratios (CR), and active insulin time (AIT). Algorithm-based decision support advising upon potential settings adjustments may enhance clinical decision-making.

Methods Single-arm, two-phase exploratory study developing decision support to commence and sustain AHCL. Participants commenced investigational MM780G, then 8 weeks Phase 1-initial optimization tool evaluation, involving algorithm-based decision support with weekly AIT and CR recommendations. Clinicians approved or rejected CR and AIT recommendations based on perceived safety per protocol. Co-design resulted in a refined algorithm evaluated in a further identically configured Phase 2. Phase 2 participants also transitioned to commercial MM780G following "Quick Start" (algorithm-derived tool determining initial AHCL settings using daily insulin dose and weight). We assessed efficacy, safety, and acceptability of decision support using glycemic metrics, and the proportion of accepted CR and AIT settings per phase**.**

Results Fifty three participants commenced Phase 1 (mean age 24.4; Hba1c 61.5mmol/7.7%). The proportion of CR and AIT accepted by clinicians increased between Phases 1 and 2 respectively: CR 89.2% vs. 98.6%, $p < 0.01$; AIT 95.2% vs. 99.3%, $p < 0.01$. Between Phases, mean glucose percentage time < 3.9mmol (< 70mg/dl) reduced (2.1% vs. 1.4%, $p = 0.04$); change in mean TIR 3.9-10mmol/L (70-180mg/dl) was not statistically significant: 72.9% ± 7.8 and 73.5% ± 8.6. Quick start resulted in stable TIR, and glycemic metrics compared to international guidelines.

Conclusion The co-designed decision support tools were able to deliver safe and effective therapy. They can potentially reduce the burden of diabetes management related decision making for both health care practitioners and patients.

*Correspondence:
Benjamin J. Wheeler
ben.wheeler@otago.ac.nz
Full list of author information is available at the end of the article

Trial registration Prospectively registered with Australia/New Zealand Clinical Trials Registry(ANZCTR) on 30th March 2021 as study ACTRN12621000360819.

Keywords Closed loop devices, Decision support tools, Glycemia, Type 1 diabetes, Continuous glucose monitoring

Background

Automated insulin delivery (AID) and advanced hybrid closed loop (AHCL) devices are the new standard for management of type 1 diabetes [1]. AHCL is characterized by the ability to deliver automated correction insulin boluses as well as basal insulin adjustments based on either predicted glucose level or deviation from setpoint [2]. In addition to automated settings, there exist a range of clinician adjustable settings depending on which commercial AID is being used [3]. With respect to the Medtronic MiniMed 780G (MM780G), these are the carbohydrate ratio (CR), active insulin time (AIT), as well as target and temporary target glucose levels [4].

These new technologies and their management may create an additional burden for healthcare teams as they strive to stay up to date in a rapidly evolving diabetes environment. This has the potential to lead to a situation where demand for AID/AHCL exceeds the supply of care. Optimal use of these systems requires the appropriate integration and formulation of available data. Adjustable settings, target glucose levels and underlying algorithms differ between devices [1, 5]. Tools such as the CARES (Calculate, Adjust, Revert, Educate, Sensor/Share) paradigm provide guidelines on how data and concepts can be integrated to provide optimal diabetes care to AID users [5]. However, access to clinicians skilled in managing these devices can vary both within and between countries, this may especially be felt in rural areas and developing economies [6].

Clinical decision support systems are data-driven tools that assist clinicians in making complicated decisions, including when to adjust clinician adjustable settings, when examining complex data sources such as AID data downloads [7]. There is limited existing literature on the effectiveness of clinical decision support systems [8, 9], and there are currently no decision support tool trials using the 780G device. Planning initial settings in transition from traditional injection or pump therapy to AHCL (known as onboarding) is another decision point for people with diabetes and their diabetes teams. This requires skill, and using decision support to help determine these has not been previously evaluated.

Therefore, this study aimed to evaluate the efficacy, safety, and tolerability of unique decision support tools to optimize use of MM780G. These tools were "Quick Start", a data-derived tool to help with determining initial AHCL system settings, and a setting optimization tool that recommended changes to ongoing insulin pump settings related to 780G AHCL including CR and AIT. These tools were evaluated with respect to both glycemic outcomes and the perceived safety of settings.

Research design and methods

Study design

This single-arm, dual-site multi-phase exploratory intervention study was conducted at University of Otago diabetes clinical trials units in Dunedin and Christchurch, New Zealand. The study was approved by health and disability ethics committee south ref (20/STH/214). The trial was also prospectively registered with Australia/New Zealand Clinical Trials Registry ACTRN12621000360819 on 30th March 2021.All participants (or their legal guardian) provided written informed consent prior to enrolment.

Participants were recruited between 29 March and 8 September 2021 and underwent a two-phase adaptive process to develop and evaluate efficacy, safety, and tolerability of an algorithm-based decision support tool to recommend AHCL settings. This was divided into two major phases: Phase 1 intervention period—initial optimization tool evaluation; and Phase 2 intervention period (preceded by Quick Start) (Fig. 1) – final optimization tool testing (following decision support algorithm adaptions learned from Phase 1).

Participants

Eligible participants were aged 7–80 years inclusive; diagnosed with type 1 diabetes with ≥ 1 year duration; on insulin pump therapy ≥ 6 months with a minimum total daily insulin dose (TDD) of ≥ 8 units. Exclusion criteria: mean glycosylated hemoglobin (HbA1c) in the prior 6 months > 10.0% (86 mmol/mol) (minimum one data point); use of a medication indicative of diabetes complications (angiotensin-converting enzyme inhibitors and statins were permitted); use of systemic glucocorticoids within 2 weeks prior to the baseline visit; current use of sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide 1 agonists; history or current evidence of significant seizure disorder, renal impairment or cardiovascular disease (including uncontrolled hypertension); severe sight threatening visual impairment; and severe neuropathy.

Demographic data (age, sex, and ethnicity) and standard anthropometric measurements were collected at

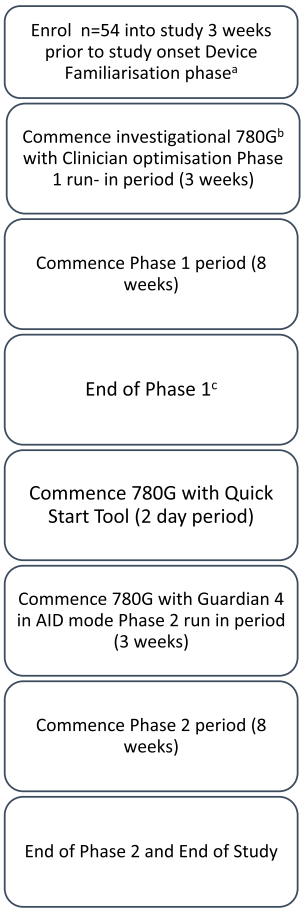

Fig. 1 Details of the different study phases. [a]A Medtronic 780G investigational device has the autocorrection algorithm found in a 780G device together with similar glucose target settings and external features as a commercial Medtronic 780G device, together with use of a Guardian 3 sensor. During this phase participants continued their prior insulin dose settings with weekly upload to Cloud and clinician review. [b]A Medtronic 780G investigational device has the autocorrection algorithm found in a 780G device together with similar glucose target settings and external features, together with use of a Guardian 3 sensor, similar to a commercial Medtronic 780G device. [c]Due to staggered recruitment of participants over several months, some participants remained in a holding pattern on investigational 780G for longer than 8 weeks in phase 1 until enrolment was complete and participants were ready to move to phase 2. In this period optimisations were provided and reviewed for safety(impact on hypoglycaemia) by the multidisciplinary team prior.

the time of baseline visit. Addresses were used to assess participant socioeconomic deprivation status using NZDep2018 [10]. NZDep2018 provides a deprivation score for mesh block geographical units defined by Statistics New Zealand. This generates a deprivation score from 1 to 10, decile one indicates the least deprived and decile ten the most deprived areas.

Study devices

Automated insulin delivery

A non-Bluetooth investigational MM780G system with Guardian 3 sensors (Medtronic Inc., Northridge, California, USA) was used for Phase 1 of the study. This device was research only tool and not commercially available. The algorithm contained within this device was similar to the commercial 780G system described below with two exceptions: the adjustable AHCL targets were limited to two options – 5.5 mmol/L (100 mg/dL) or 6.7 mmol/L (120 mg/dL), and Guardian 3 (calibration requiring) sensors were used instead of Guardian 4. For phase 2, commercial MM780G with Guardian 4 calibration-free sensors were used. In these devices adjustable AHCL glucose targets were 5.5 mmol/L (100 mg/dL), 6.1(110mg/dl) or 6.7 mmol/L (120 mg/dL).

Optimization decision support tool

A mathematical model-based digital twin (DT) tool was used to personalize and automate AHCL settings.

DT is a mathematical model of the participant's glucose dynamics as function of insulin delivery and carbohydrates intake. It enables current settings to be analyzed and is the basis for optimization derived insulin settings as delivered below. The tool uses a minimum of 14 consecutive days of sensor augmented pump glucose data and insulin settings to generate the following AHCL setting recommendations: 3-h blocks for carbohydrate ratios (00:00– 03:00, 03:00–06:00 etc.); with a single recommended weekly AIT setting.

Participants uploaded their insulin pump data on a weekly basis throughout the study. This data resulted in a series of recommendations using the optimization algorithm for insulin dosing and pump setting alterations that were then reviewed by study endocrinologists (B.W., M.D.B., S.S.). These reviews were conducted in an objective manner as the specialists listed were not involved in the development of any optimization tools.

Insulin dose settings were rejected after case review only if they were perceived to result in an increased risk of hypoglycemia < 3.9 mmol/L. Two separate variants of this tool were tested in the Phase 1 testing intervention period and phase 2 intervention period, with the latter being a modified tool following co-design.

Quick Start tool

Based on the participant's body weight and prior TDD, this decision support tool was used at the start of the phase 2 intervention period to guide transition to the commercial MM780G. Prior settings on the investigational system were disregarded. The QuickStart tool provided an initial set of standard settings pump

settings i.e., carb ratio, insulin sensitivity factor, basal rates, and AIT.

Device initiation and familiarisation (3-weeks)

As shown in Fig. 1, at the enrolment visit the study device, and training (including in therapy management software [Medtronic, Northridge, CA]) was provided to participants. All participants were provided with standard refresher training on management of hypoglycemia and ketones. Weekly clinician optimised settings adjustments in predictive low glucose management (PLGM) were delivered in this phase, as the AHCL algorithm had not yet been activated.

Phase 1 run- in period (3-weeks)

As shown in Fig. 1, at the beginning of phase 1 run-in, an in-person study visit occurred and AID with AHCL was activated. All pump settings were determined by clinicians at this time point. For the next three weeks, weekly remote data review occurred with settings adjustments as required communicated by phone. Sensor Glucose data was reviewed again to check accuracy and protocol adherence. The duration of this phase was 3 weeks.

Phase 1 intervention period (8-weeks)

Phase 1 provided feasibility data on the decision support algorithm and allowed co-design to improve function to be subsequently further investigated in Phase 2. Algorithm derived weekly recommendations for AHCL settings were provided as detailed in Supplementary file 1. Study clinicians reviewed recommendations and either fully accepted or partially rejected based on perceived hypoglycemia safety. Adjustments were then communicated remotely to participants by phone.

During phase 1, the study investigators and Medtronic engineers discussed progress fortnightly as part of a co-design process to assess and adapt the algorithm for efficacy and safety. In these meetings, the clinical rationale of recommendations not accepted was discussed.

A key part of the underlying optimization algorithm was the entering of meal boluses at regular intervals, indeed optimization settings were not delivered for the week if less than 2 meals per day in a 2-week period were bolused for.

As participants were recruited sequentially, and all needed to move to phase 2 at the same time, some participants spent more time on investigational MM780G following 8-weeks of phase 1 while they awaited all participants in the first phase to complete a minimum of 8 weeks of phase 1 intervention. Therefore, the total duration of the full study, including non-optimized phases, varied between 46 and 52 weeks.

As demonstrated in the supplementary file, the Smartguard Glucose settings were entirely at clinician discretion with the default at 5.5mmol/100mg/dl, this was increased to 6.7 mmol/121mg/dl if the TBR was > 4% and then reverted to 5.5mmol when TBR returned to target levels.

Phase 2 run-in and intervention period

Phase 2 assessed efficacy, safety, and acceptability of the final co-designed algorithm (Fig. 1). This phase also marked a transition between investigational AHCL to commercial AHCL (devices as described above). Phase 2 was also preceded by the QuickStart standalone onboarding decision support tool (described above). All other Phase 2 procedures were as per Phase 1, including the 3-week clinician derived settings optimization followed by weekly algorithm derived settings recommendations, which were reviewed by clinicians in an identical manner to phase 1 and approval or rejected using identical rationale.

As in phase 1 Smartguard Glucose settings were entirely at clinician discretion with the default at 5.5mmol/100mg/dl, this was increased to 6.1/ 110mg/dl and could potentially increase to 6.7mmol /121mg/dl if the TBR was > 4% and then reverted to 5.5mmol when TBR returned to target levels.

Objectives

This study had multiple primary endpoints including the efficacy of the decision support tool determined in both phases by comparing mean TBR (< 3.9mmol [< 70mg/dl) and mean TIR (3.9–10 mmol [70–180 mg/dL)) from the first 8 weeks of the phase 1 intervention period compared to the 8 weeks of the Phase 2 intervention period.

To assess perceived safety, and acceptability of the optimization testing tool, the proportion of total recommendations accepted during both study intervention phases were analyzed.

In addition to those, evaluation of the following glycemic variables, consistent with the international consensus statement [11]: mean glucose; time in severe hypoglycemia < 3.0 mmol/L (< 54 mg/dL); time above range (TAR) > 10 mmol/L (> 180 mg/dL) including readings of > 13.9 mmol/L (≤ 250 mg/dL); and time in severe hyperglycemia.

For the Quick Start tool, a similar set of glycemic metrics (in particular time below range [TBR] and TIR) were evaluated for participants for the first 14 days after the phase 2 run in period as descriptive statistics.

Proportion of participants meeting clinically significant glycemic targets (TIR > 70% and TBR < 3.9 mmol/L) were analyzed for phase 1 and 2, as well as percentage time spend in auto-mode during both phases.

Safety assessment

The safety of both the Quick Start tool and the optimization tools were evaluated using multiple parameters. Adverse events were categorized by event type (severe hypoglycemia, diabetic ketoacidosis, hospitalization), with the frequency of events reported by event category. Severe hypoglycemia was characterized by the presence of a glucose level of 3 mmol/L (54 mg/dL) and severe cognitive impairment requiring external assistance for recovery. Diabetic ketoacidosis was defined according to standard guidelines [12].

Statistical analysis

All statistical analyses in this study were conducted based on the three hypotheses as stated below.

> Hypothesis 1: The TBR < 3.9mmol for study participants is lower during phase 2 (optimization testing) compared with phase 1 (the feasibility phase).
> Hypothesis 2: The percentage of accepted settings related to AHCL (Carb ratio and AIT) will improve during phase 2 compared with phase 1.
> Hypothesis 3: TIR (3.9-10mmol) for study participants is improved during phase 2 compared with phase 1.

We further analyzed the Glycemic control outcomes in a descriptive manner 2 weeks following Quick start implementation.

The proportion of overall accepted settings, as well as non-automated settings (basal rate and insulin sensitivity factor) were also compared between phase 1 testing and phase 2 testing intervention periods.

All results were analyzed on a modified intention-to-treat basis with all data being included in final analysis as available. Results were adjusted for multiple comparisons using the Benjamani Hochberg approach [13]. Stata 17 (Stata Corp, Texas, USA) was used for statistical analysis. A p-value < 0.05 was considered statistically significant. Result reporting was conducted according to the CONSORT 2010 statement extension for the reporting of clinical trials.

Continuous variables, including TBR and TIR, are reported as mean and standard deviation, by time of assessment, and changes over time were calculated with the corresponding 95% confidence interval (CI). Changes were compared against the null hypothesis (no change) using a two-sample t test. The Chi-squared test was used to analyze binary or categorical variables (proportion-based statistics).

Sample size

This was an exploratory study. Before the study commenced a study sample size of 60 was initially decided upon pragmatically and given that a sample size of 60 was able to provide 95% power at a two-sided alpha of 0.05 to detect an effect size (Dz) of 0.47. Assuming that participants' change in time in range (TIR) has a standard deviation of 8.5, this represented an absolute improvement of 4.0 percentage points (ie. from 70 to 74% TIR). Subsequently safety (hypoglycaemia) and acceptability were also deemed of priority. For these purposes the current sample size was deemed sufficient to detect moderate effects in both these measures.

Results

A total of 53 participants were enrolled, completed the device initiation and familiarization, and commenced phase 1 (Table 1). All were prior pump users but only 65% had used CGM. Three participants withdrew during phase 1 intervention and 50 participants proceeded to Quick Start implementation and phase 2 (Fig. 2).

Table 1 Demographic and clinical characteristics of the study population at baseline

Variable	Participants ($n = 54$)
Age, years	24.4 ± 15.3
Female sex, n (%)	33 (61.1)
Body mass index (adults), kg/m^{2}[a]	27.2 ± 6.7
Body mass index z-score[b] (children [c])	0.87 ± 0.89
Glycosylated hemoglobin, mmol/mol (%)	61.5±9.7 (7.7±0.7)
Duration of type 1 diabetes, years	12.1±9.4
Duration of pump use, years	7.3 ± 4.7
Total daily dosage of insulin, units	47.1 ± 25.8
Continuous glucose monitoring use prior to study, n (%)	35(64.8%)
Intermittently scanned	18 (33.3)
Real-time CGM	17 (31.5)
Diabetes-related complications, n (%)	5 (9.3)
Severe hypoglycemia admissions	0 (0)
Microalbuminuria, n (%)	3 (5.6)
Retinopathy, n (%)	2 (3.7)
New Zealand Deprivation Index 2018[d]	4.4 ± 2.7

Values mean ± standard deviation, or number of participants (%)

[a] Adult was defined as age ≥ 16 years $n = 35$

[b] z-score (or standard deviation score) indicates the number of standard deviation units above or below the mean body mass index for age and sex of a reference population

[c] children were defined as being aged < 16-year $n = 19$

[d] The NZDep is an area-based measure of socioeconomic deprivation in New Zealand. Decile 1 indicates least deprived while decile 10 represents the most deprived areas

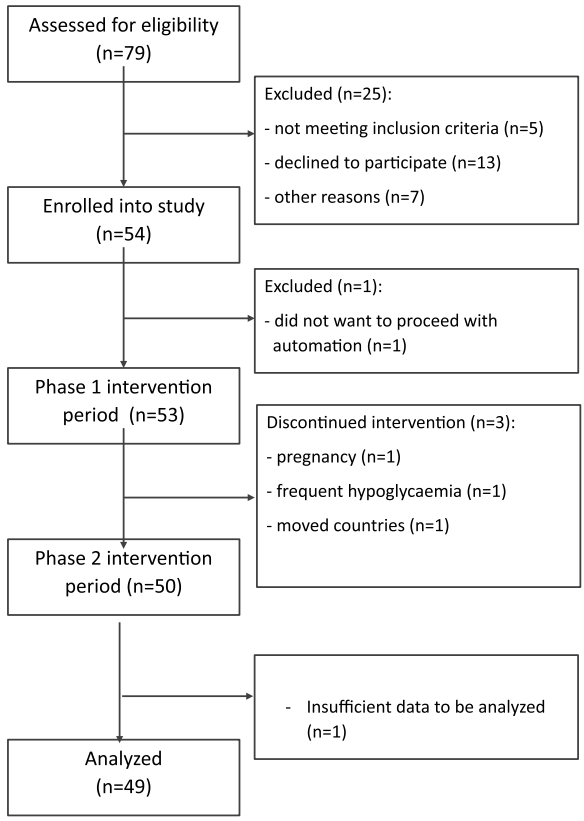

Fig. 2 Participant flow through the study

Glycaemic outcomes comparing throughout each study period

Glycemic outcomes collected during the Phase 1 run in period represented participants' baseline glycemic control whilst in AHCL. When compared to international guidelines [14], the mean results for all glycemic parameters in this run-in period fall within guideline directed targets. There was strong evidence of a reduction in both hypoglycemia(< 3.9mmol)($P = 0.04$) and severe hypoglycemia(< 3.0) ($p < 0.01$) across intervention phases as shown in Table 2.

Acceptability: The proportion of accepted settings—carb ratios and active insulin time

As shown in Table 3, there was evidence of an increase in the total proportion of accepted AHCL settings, that improved following the Phase 2 intervention period, 98.9% vs. 92.2%, $p < 0.001$. When looked at separately, the proportion of accepted settings for carbohydrate ratio for the 50 participants in the Phase 2 testing intervention period compared to Phase 1 intervention improved, 98.6% vs, 89.2%, $p < 0.01$; as did the proportion of accepted settings for AIT, 99.3% vs,95.2%, $p < 0.001$.

Efficacy: Achieving target glycaemic control

Compared to baseline, the proportion of participants achieving a TIR > 70% was largely stable across all phases. TIR > 70% increased from 59.6% at baseline to 63.5% during phase 1, before falling to 59.2% at the end of the phase 2 intervention period. In terms of time below range only 2% of participants had a time below range > 4% at the end of the phase 2 intervention period.

Quick start phase

As described in Table 4, The TIR for 2 weeks following Quick start phase was 70.3%, with a TBR < 70mg/dl of 1.8% and a Time Above range (TAR) of 27.9%. All mean parameters were within the international consensus guidelines with the exception of TAR > 13.9mmol (> 250mg/dl), which was at 6.8% where the consensus recommended target is 5% as well as TAR > 10mmol, where the target is 25% [14]. The percentage of time in AHCL was 78.5% and percentage of time that the sensor was active was 88.1%, the average number of AHCL exits per week was 0.8.

Duration of active insulin time and AHCL glucose targets

As shown in Table 5, an AIT of 2 h was more likely in the Phase 2 testing intervention period compared to phase 1 intervention period (98.0% vs. 59.1%, $p < 0.01$). In terms of AHCL targets selected by clinicians, there was no difference in the likelihood of having a target of 5.5mmol/100mg/dl in either intervention period (96.4 vs. 94.8%, $p = 0.5$).

Safety outcomes

There were four documented serious adverse events, all of which occurred in the phase 1 intervention period, with no adverse events occurring in the Phase 2 testing intervention period phase. All were deemed unrelated to decision support. Two events (3.8%) resulted in hospitalization, including an episode of gastroenteritis without ketosis and one of diabetic ketoacidosis (due to infusion site failure). The other two adverse events that did not result in hospitalization included an episode of hyperglycemia without ketosis and severe hypoglycemia requiring the assistance of a family member due to insulin/carbohydrate intake mismatch. None of the adverse events were related to device malfunction.

Discussion

This study evaluated the impact of decision support tools to safely maintain clinical outcomes over an extended period in a cohort of experienced pump users. Importantly, time in range was maintained with

Table 2 Glycaemic outcomes[a] for all phases of study

	Run in	Phase 1 intervention	Phase 2 intervention	*P* value Phase 2 vs. Phase 1
Mean glucose, mmol/L	8.4 ± 0.8	8.3 ± 0.6	8.5 ± 0.7	0.5
Glucose management indicator, %[b]	6.9 ± 0.4	6.9 ± 0.2	7 ± 0.3	0.5
Coefficient of variation, %	35.8% ± 5	36.3 ± 4.7	34.2 ± 5	0.08
%time in severe hypoglycemia (< 3 mmol/L/54mg/dl),	0.40 ± 0.40	0.40 ± 0.40	0.10 ± 0.10	**0.01**
%Time below range (< 3.9 mmol/L/70mg/dl)[b]	2.1 ± 1.70	2.10 ± 1.30	1.40 ± 1.20	**0.04**
% Time in tight range (3.9–7.8mmol/70-140mg/dl)	49.7 ± 10.4	50.2 ± 7.2	49.2 ± 7.7	**0.55**
%Time in range (3.9–10 mmol/L/70-180mg/dl)[c]	72.2 ± 9.9	72.9 ± 7.8	73.5 ± 8.6	0.84
%Time above range (>10mmol/180mg/dl)	25.7 ± 10.0	25 ± 7.3	25.2 ± 8.5	0.87
%Time in severe hyperglycemia (> 13.9 mmol/L/ > 250mg/dl)	6.4 ± 5.8	6.2 ± 3.9	6.1 ± 4.4	0.91
Total Daily dose, units	51.6 ± 30.4	51.3 ± 29.2	47.1 ± 19.3	0.46
Meal Bolus, units	19.6 (12.4)	19.3 ± 10.9	14.8 ± 8	0.06
Basal insulin, units	23.1 (11.9)	20.1 ± 11.2	16.7 ± 7.8	0.13
Autocorrection, units	8.2 (7.1)	9.7 ± 7.2	10.7 ± 6.3	0.58
Meals per day	5.2 ± 2	5.1 ± 1.8	4.6 ± 1.8	0.32
Carbs per day(g)	174.3 ± 70.7	169.8 ± 71.4	156.8 ± 71.8	0.51
Sensors use %	89.8 ± 11.8	87.6 ± 9.9	88.6 ± 15.6	0.73
% Time in Automode[c]	94.1 ± 5.7	95.8 ± 6.3	98.1 ± 3.9	0.07
AHCL exits, week[d]	1.2 ± 1	1.1 ± 0.90	0.7 ± 0.40	0.05
% of Subjects Automode < 70%	3.8%	1.9%	0%	0.07

[a] Iinternational consensus group targets [14]: TIR (3.9-10mmol/70-180mg/dl) > 70%, TBR (< 3.9mmol/ < 70mg/dl) < 4%, TBR(< 3.0mmol < 54mg/dl) < 1%, TAR (> 10mmol/180mg/dl) < 25%, (> 13.9mmol/250mg/dl) < 5%

[b] (GMI)Glucose Management Indicator, a measure converting mean sensor glucose into an estimated Hba1c Value [15]

[c] *p* value comparing phase 1 to phase 2

[d] number of exits from OL for different reasons per week expressed as average and standard deviation

Table 3 Total Numbers and Proportions of Accepted and Non-Accepted Settings in all of Phase

	Phase 1 intervention	Phase 2 intervention	*P*-Value
	Accepted	**Accepted**	
Automation settings			
Carbohydrate Ratio	297/333(89.2%)	275/279(98.6%)	**< 0.01**
Active Insulin Time	317/333(95.2%)	277/279(99.3%)	**< 0.01**
All Automation settings	614/666(92.2%)	552/558 (98.9%)	**< 0.01**

a mean > 70% throughout both phases, and Phase 2 final algorithm showed reduction in hypoglycemia compared to Phase 1. Following the algorithm adjustments of co-design, expert clinician perceptions of safety and acceptability of CR settings and AIT settings also improved between phases and reached near 100% acceptability by end of phase [2].

In terms of glycemic control outcomes in this study, mean TIR remained stable throughout both intervention phases. In addition, both the TBR(< 3.9mmol/L and time in severe hypoglycemia (< 3 mmol/L [< 54 mg/dL]) were lower (in both phases) than real-world studies published in the last 5 years [16, 17]. Following both intervention phases, the proportion of participants meeting clinical consensus group targets for TIR remained stable between 59.2% and 63.5%, whereas those meeting the hypoglycemia target (< 3.9mmol) increased to more than 98% at the end of the second intervention phase. The results for both of these parameters, at the end of the study compare favorably with both interventional studies and large real-world studies [18]. This highlights the potential of the optimization testing decision support tool to maintain

Table 4 Glycemic outcomes 2 weeks following Quick Start implementation

Parameter	Following Quick Start
Mean glucose, mmol/L	8.5 ± 0.9
Glucose management indicator, %	7.0 ± 0.4
Coefficient of variation, %	35 ± 5
%Time in severe hypoglycemia(< 3 mmol/L [54mg/dl]),	0.1 ± 0.2
%Time below range (< 3.9 mmol/L [70mg/dl])	2.1 ± 1.7
%Time in range (3.9–10 mmol/L [70-180mg/dl]),	70.3 ± 10.4
Time above range (> 10 mmol/L [180mg/dl]),	27.9 ± 10.5
Time in severe hyperglycemia (> 13.9 mmol/L > 250mg/dl),	6.8 ± 5.1
Auto Mode percentage	78.5 ± 5.7
Total daily insulin dose,	47 ± 21.1
Sensors use, %	88.1 ± 8.2
AHCL exits per week, n	0.8 ± 0.5

HbA1c glycosylated hemoglobin

Table 5 Proportion of actual AIT and AHCL settings at each study visit, compared to those recommended(Phase 1 and Phase 2 intervention periods)

Settings	Phase 1 intervention period	Phase 2 intervention period	*P*-value
Active insulin time = 2 h[a]	250(59.1%)	385(98.0%)	**< 0.01**
Active insulin time > 2 h	173(40.9%)	8(2%)	
Smart Guard target = 5.5 mmol/L (100 mg/dL)[b]	401(94.8%)	377(96.4%)	0.5
Smart Guard target > 5.5 mmol/L (> 100 mg/dL)	22(5.2%)	14(3.6%)[c]	

[a] recommended AIT = 2 h

[b] recommended AHCL targets = 5.5mmol

[c] 10 settings were 6.1mmol target, 4 were at 6.7mmol

TIR while reducing the incidence of severe hypoglycemia episodes and non-severe hypoglycemia, both of which have historically complicated attempts to intensify glucose control [14]. Previous decision support tool trials of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) have not achieved this magnitude of reduction of hypoglycemia [8, 9].

The clinician acceptability of optimisation derived insulin doses improved overall in phase 2 compared to phase 1, with all automation settings (carb ratio and AIT settings) being accepted by the end of the Phase 2 testing intervention phase. This occurred in the context of an identical level of clinician intervention across all phases, which may have contributed to the observed lowering of TBR at the end of phase 2. In contrast, decision support programs such as the KNDSS reported 67.9% agreement with some recommendations and only 41–45% agreed with all recommendations [9]. Furthermore, all participants had an AIT of 2 h and a AHCL target of 5.5mmol(100mg/dl) at study end. These indicate that the decision support tool was able both to offer settings that were safe, acceptable to clinicians and sufficiently effective to reduce hyperglycaemia. Previous studies have evaluated a small number of individuals using either investigational AID devices [19, 20] MDI alone [21] or mixed MDI and pump therapy [22, 23].

Decision making around initial AHCL settings is an important and common clinician challenge for diabetes teams. The Quick Start tool was a novel approach to commencing insulin dosing with AHCL. Previous approaches to calculating the starting dose of insulin have been either empiric or weight based. With Quick Start, the TDD was based on a derived TDD that resulted from the TDD used in the optimization feasibility phase. Overall, at the end of 2 weeks of follow up TIR and other glycemic parameters except for TAR > 13.9mmol all fell within international guidelines targets [11] and no safety concerns were seen. This appears a simple a feasible approach to commencing AHCL.

During the testing phase, there was a transition from calibration requiring (Guardian 3) sensors to calibration free/reduced (Guardian 4) sensors. This was manifested

by both increased time in AHCL and increased sensor use percentage in the Phase 2 testing intervention period compared to the phase 1. Other real-world studies to evaluate the Guardian 4 sensor found no difference in glycaemic outcomes but less patient involvement in the form of BGL testing was required. Recently published quantitative and qualitative work has also found that people using calibration free sensors find reduced burden, as well as enhanced trust and perceived improved overall quality of life using AHCL [24, 25]. Future studies, including longer term observational studies may be needed to evaluate if the benefits of increased usability, time in AHCL and participant satisfaction lead to improved glycaemic control.

The optimal frequency of dosing advice provided by previous studies using decision support tools ranged from bi-weekly to every three weeks. In contrast to the simulation trials of Breton [21] and Tyler [9], our participants used the optimization tools in real-world conditions. Potential clinical application of these tools could be in primary care or large secondary care clinics, and in developing countries with reduced access to specialist diabetes care. Moreover, a variant of the Phase 2 intervention period decision support tool can be used by experienced AHCL users who wish to self-titrate their insulin doses to optimize glycemic control.

The long duration of the study (26 weeks) was a relative strength as this study was longer than previous studies evaluating decision support tools. Unlike a previous trial by Bisio et al., our cohort of participants sustained a high level of upload and clinician input throughout the trial with very few withdrawals [24]. With respect to overall safety, there were few serious adverse events during the current study, and those that were documented occurred during the first optimization phase. This suggests that there is little added risk in the expanded use of an optimization algorithm, even by non-specialist clinicians or in areas where access to specialist diabetes care is limited.

The limitations of this study include its sample size and the relative demographic homogeneity of the participants. Therefore, the study findings may not be generalizable to more ethnically diverse populations. Further the introduction of the Guardian 4 sensor may have contributed to the glycemia data in phase II. This study occurred at a time where many automated insulin delivery devices were evolving to use calibration free sensors, which were gaining regulatory approval worldwide. As such we were bound ethically to deliver these sensors to participants. While calibration free sensors can potentially increase the time in automode and therefore potentially the time in range, for both this and another observational study [26] this was not the case. Study participants were also supported by a clinical team with extensive experience, and the participants had generally good glycemia at baseline. A decision support tool as utilized in this study may be of more use in situations where there is limited experience and confidence in maximising the benefit of the 780G, or work-force limitations preclude early review of glycemia and setting titration in the event of not reaching glycaemic targets.

As discussed in methods, whilst consistent bolusing was a pre-requisite of optimisation settings being delivered, we did not formally evaluate the accuracy of carbohydrate countingFuture studies could evaluate more evolved optimization algorithms together with closer examination of bolus behavior (as discussed above) to determine whether overall glycemic control can be improved.

Further research, using studies specifically designed to assess manual mode control in terms of basal rates and ISF settings would help guide practice, especially for those participants that struggle to maintain automode/ are in automode less than 70% of the time.

Conclusions

This is the first intervention trial in type 1 diabetes to evaluate the efficacy, safety, and acceptability of decision support tools for initiating and sustaining glycemic control in individuals using an AHCL device. The use of decision support tools to initiate and sustain AHCL therapy maintained glycemic control, and hypoglycemia was reduced. In addition to being safe, the decision support tools generated insulin doses and pump settings that were deemed clinically acceptable by experienced clinicians. Overall, decision support tools have the potential to act as digital enhancers of care to augment the role played by experienced diabetes clinicians in sustaining target glycemic control in AHCL users.

Abbreviations

AHCL	Advanced Hybrid Closed Loop.
TDD	Total Daily Dose
CR	Carbohydrate Ratios.
AID	Automated Insulin Delivery
AIT	Active Insulin Time
DT	Digital Twin
ISF	Insulin Sensitivity Factor
HbA1c	Glycosylated hemoglobin
NZDep	NZ Deprivation Index score
ANZCTR	Australia and New Zealand Clinical Trials Register

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01709-y.

Supplementary Material 1.

Acknowledgements

We would like to acknowledge the ongoing support provided by our participants in both study phases. Professional editing assistance was provided

by Nicola Ryan, independent medical writer. Medtronic Inc. provided study devices and funded the single-arm interventional trial that the participants were drawn from, and Medtronic systems engineers were involved in the design of the optimization algorithms. Funding for the writing and dissemination of this paper was provided by the Health Research Council NZ grant 22/051.

Authors' contributions
S.S. produced the first draft of the manuscript, and all authors worked collaboratively to review and prepare the final manuscript. S.S., B.J.W., M.D.B., B.G., N.K. and M.J. were involved with the design of the study and its protocol. C.F., A.W., S.J. and V.G. contributed to recruitment, retention, and completion of study visits. S.S., B.J.W. and M.D.B. conducted the patient visits and data processing. A.B. and S.S. conducted the statistical analysis with supervision from J.W.

Author information
Not Applicable.

Funding
Medtronic Inc. provided study devices and funded the single-arm interventional trial that the participants were drawn from, and Medtronic systems engineers engaged in the design of the optimization algorithms. Funding for the writing and dissemination of this paper was provided by the Health Research Council NZ grant 22/051.

Availability of data and materials
The data that support the findings of this study are available from Medtronic,inc but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Medtronic, inc.

Declarations

Ethics approval and consent for publication
The study was approved by health and disability ethics committee south ref (20/STH/214). All participants (or their legal guardian) provided written informed consent prior to enrolment.

Consent for publication
Not Applicable.

Competing interests
S.S., S.J. and C. F. have no conflicts of interest to disclose. B.J.W. has previously received research funding from Dexcom, Medtronic and iSENS. M.D.B. has received research funding from Novo Nordisk, Medtronic, Dexcom and Pfizer, research support from Medtronic, Dexcom and SOOIL, and honoraria from Medtronic. The following co-authors have no conflicts of interest (B.G., J.W., N.K., V.G., A.B., M.J., A.W. and B.T.).

Author details
[1]Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, 201 Great King St, Dunedin, Otago 9016, New Zealand. [2]Department of Endocrinology and Diabetes, North Shore Hospital, Te Whatu Ora Waitemata , Auckland, New Zealand. [3]Department of Paediatrics, Te Whatu Ora Waitaha, Christchurch, New Zealand. [4]Department of Paediatrics, University of Otago, Christchurch, New Zealand. [5]Medtronic Inc, Northeast Minneapolis, 710 Medtronic Parkway, Minneapolis, MN, USA. [6]Department of Paediatrics, Te Whatu Ora Southern, Dunedin, New Zealand.

Received: 17 April 2024 Accepted: 27 August 2024
Published online: 30 August 2024

References
1. Leelarathna L, Choudhary P, Wilmot EG, Lumb A, Street T, Kar P, et al. Hybrid closed-loop therapy: Where are we in 2021? Diabetes Obes Metab. 2021;23(3):655–60.
2. Carlson AL, Sherr JL, Shulman DI, Garg SK, Pop-Busui R, Bode BW, Lilenquist DR, Brazg RL, Kaiserman KB, Kipnes MS, Thrasher JR. Safety and glycemic outcomes during the MiniMed™ advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2022;24(3):178–89. https://doi.org/10.1089/dia.2021.0319.
3. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med. 2019;381(18):1707–17.
4. Phillip M, Nimri R, Bergenstal RM, Barnard-Kelly K, Danne T, Hovorka R, et al. Consensus recommendations for the use of automated insulin delivery technologies in clinical practice. Endocr Rev. 2023;44(2):254–80.
5. Messer LH, Berget C, Forlenza GP. A clinical guide to advanced diabetes devices and closed-loop systems using the CARES paradigm. Diabetes Technol Ther. 2019;21(8):462–9.
6. Lu H, Holt JB, Cheng YJ, Zhang X, Onufrak S, Croft JB. Population-based geographic access to endocrinologists in the United States, 2012. BMC Health Serv Res. 2015;15(1):1–13.
7. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med. 2020;3(1):17.
8. Nimri R, Battelino T, Laffel LM, Slover RH, Schatz D, Weinzimer SA, et al. Insulin dose optimization using an automated artificial intelligence-based decision support system in youths with type 1 diabetes. Nat Med. 2020;26(9):1380–4.
9. Tyler NS, Mosquera-Lopez CM, Wilson LM, Dodier RH, Branigan DL, Gabo VB, et al. An artificial intelligence decision support system for the management of type 1 diabetes. Nat Metab. 2020;2(7):612–9.
10. Atkinson J, Salmond C, Crampton P. NZDep2018 index of deprivation, final research report. Wellington: University of Otago; 2020.
11. Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinol. 2023;11:42.
12. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335–43.
13. Ferreira JA. The Benjamini-Hochberg Method in the Case of Discrete Test Statistics. Int J Biostat. 2007;3(1):11. https://doi.org/10.2202/1557-4679.1065.
14. Nathan DM, Group DER. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2014;37(1):9–16.
15. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. Diabetes Care. 2018;41(11):2275–80.
16. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. The Lancet. 2018;392(10155):1321–9.
17. Da Silva J, Lepore G, Battelino T, Arrieta A, Castañeda J, Grosman B, et al. Real-world performance of the MiniMed™ 780G system: first report of outcomes from 4'120 users. Diabetes Technol Ther 2021(ja).
18. Grassi B, Gómez AM, Calliari LE, Franco D, Raggio M, Riera F, et al. Real-world performance of the MiniMed 780G advanced hybrid closed loop system in Latin America: substantial improvement in glycaemic control with each technology iteration of the MiniMed automated insulin delivery system. Diabetes, Obes Metab. 2023;25:1688.
19. Palisaitis E, El Fathi A, Von Oettingen JE, Krishnamoorthy P, Kearney R, Jacobs P, et al. The efficacy of basal rate and carbohydrate ratio learning algorithm for closed-loop insulin delivery (artificial pancreas) in youth with type 1 diabetes in a diabetes camp. Diabetes Technol Ther. 2020;22(3):185–94.
20. Dassau E, Pinsker JE, Kudva YC, Brown SA, Gondhalekar R, Dalla Man C, et al. Twelve-week 24/7 ambulatory artificial pancreas with weekly adaptation of insulin delivery settings: effect on hemoglobin A1c and hypoglycemia. Diabetes Care. 2017;40(12):1719–26.
21. Breton MD, Patek SD, Lv D, Schertz E, Robic J, Pinnata J, et al. Continuous glucose monitoring and insulin informed advisory system with automated titration and dosing of insulin reduces glucose variability in type 1 diabetes mellitus. Diabetes Technol Ther. 2018;20(8):531–40.

22. Avari P, Leal Y, Herrero P, Wos M, Jugnee N, Arnoriaga-Rodríguez M, et al. Safety and feasibility of the PEPPER adaptive bolus advisor and safety system: a randomized control study. Diabetes Technol Ther. 2021;23(3):175–86.
23. Reddy M, Pesl P, Xenou M, Toumazou C, Johnston D, Georgiou P, et al. Clinical safety and feasibility of the advanced bolus calculator for type 1 diabetes based on case-based reasoning: a 6-week nonrandomized single-arm pilot study. Diabetes Technol Ther. 2016;18(8):487–93.
24. Bisio A, Anderson S, Norlander L, O'Malley G, Robic J, Ogyaadu S, et al. Impact of a novel diabetes support system on a cohort of individuals with type 1 diabetes treated with multiple daily injections: a multicenter randomized study. Diabetes Care. 2022;45(1):186–93.
25. Grosman B, Wu D, Miller D, Lintereur L, Roy A, Parikh N, et al. Sensor-augmented pump-based customized mathematical model for type 1 diabetes. Diabetes Technol Ther. 2018;20(3):207–21.
26. Matejko B, Juza A, Kieć-Wilk B, Cyranka K, Krzyżowska S, Cohen O, et al. One-year follow-up of advanced hybrid closed-loop system in adults with type 1 diabetes previously naive to diabetes technology: The effect of switching to a calibration-free sensor. Diabetes Technol Ther. 2023;25:554.

Publisher's Note